A PROSPECTIVE, RANDOMIZED, OPEN LABEL, COMPARATIVE STUDY OF D-CHIROINOSITOL WITH METFORMIN IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME

Dissertation submitted to

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DR. M.G.R. MEDICAL UNIVERSITY

In partial fulfillment for the award of the degree of

DOCTOR OF MEDICINE

IN

PHARMACOLOGY

INSTITUTE OF PHARMACOLOGY

MADRAS MEDICAL COLLEGE

CHENNAI - 600 003

MAY 2018

CERTIFICATE

This is to certify that the dissertation entitled, **"A PROSPECTIVE, RANDOMIZED, OPEN LABEL, COMPARATIVE STUDY OF D-CHIROINOSITOL WITH METFORMIN IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME"** submitted by Dr.R.M.RAJESHWARE, in partial fulfillment for the award of the degree of Doctor of Medicine in Pharmacology by The Tamilnadu Dr.M.G.R.Medical University, Chennai is a Bonafide record of the work done by her in the Institute of Pharmacology, Madras Medical College during the academic year 2015 - 2018.

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DECLARTATION

I, Dr.R.M.Rajeshware, solemnly declare that the dissertation titled **"A PROSPECTIVE, RANDOMIZED, OPEN LABEL, COMPARATIVE STUDY OF D-CHIROINOSITOL WITH METFORMIN IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME"** has been prepared by me and submitted to the Tamilnadu Dr.M.G.R.Medical University, Chennai in partial fulfillment of the rules and regulations for the M.D degree examination in Pharmacology.

Place : Dr. R.M.Rajeshware

Date:

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PLAGIARISM CERTIFICATE

This is to certify that this dissertation work titled **"A PROSPECTIVE, RANDOMIZED, OPEN LABEL COMPARATIVE STUDY OF D-CHIROINOSITOL WITH METFORMIN IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME"** of the candidate Dr.R.M.RAJESHWARE with Registration number 201516004 for the award of the **Degree of Doctor of Medicine in the branch of Pharmacology**. I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains pages from introduction to conclusion and shows **two percentage (2%)** of plagiarism in the dissertation.

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TABLE OF CONTENTS

INTRODUCTION

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder of women of reproductive age group affecting approximately, 4 – 15 % of female population. PCOS is a complex heterogenous disorder with features of oligomenorrhoea, anovulation, and signs of androgen excess like hirsutism, acne, male type baldness and multiple cysts in ovaries. It is the most common cause of infertility due to menstrual dysfunction. [1]

PCOS is of multifactorial etiology and attributed to familial, genetic and environmental factors. Familial occurrence is noted among siblings (sisters) and offspring (female children). Environmental factors like stress, life style changes including increased fat and carbohydrate diet and reduced physical activity are important contributing factors. [1,2] Genetic factors include mutations in genes coding for CYP450 enzymes like CYP 11A1, CYP 21A1 and defects in enzymes involved in cholesterol metabolism and androgen synthesis.

Diagnosis is based on consensus at Rotterdam (2003) : oligo / anovulation, hyperandrogenism, polycystic ovaries, with exclusion of other endocrine disorders. [3]

Anovulation in PCOS is due to inappropriate gonadotropin secretion. This leads to preferential production of luteinizing hormone (LH) compared to follicle stimulating hormone (FSH) [1,7] and LH:FSH ratio becomes 2:1 or even 3:1[4] .

Insulin resistance is common in approximately 60 – 70% of women with PCOS. [5,6] IR is reduced response of peripheral tissues to insulin. It is due to phosphorylation of serine residues of insulin receptor leading to post binding abnormality in receptor mediated signal transduction.

IR is sensed by pancreas as insulin deficiency and leads to compensatory hyperinsulinemia. This excess insulin stimulates luteinizing hormone (LH) to produce more androgens from theca cells of ovary leading to features of hyperandrogenism. Increased androgens, prevent maturation of one dominant follicle as Graafian follicle and also prevent apoptosis of small follicles, which are normally destined to disappear. This gives the appearance of polycystic ovaries in ultrasound as necklace like pattern in the peripheral rim of ovary. [7]

Complications of PCOS include infertility, risk of endometrial and breast cancers in later life. Metabolic complications include type 2 diabetes mellitus, obesity, dyslipidemia, atherosclerosis, coronary artery disease together called as metabolic syndrome or syndrome X. [8] Thus, PCOS is not a disease of short term effects but a syndrome of long term consequences. [9]

Treatment depends on age of the patient and clinical features. Unmarried, adolescent girls with hyperandrogenism need anti androgens and hormonal contraceptives for cycle regularization. Married women with infertility need ovulation induction. [10] In addition, life style modifications like regular exercise and balanced diet are the first line management. Insulin sensitizers like metformin are used to avoid and

treat metabolic disorders associated with IR such as diabetes, dyslipidemia and cardiovascular events. But this is associated with gastrointestinal adverse effects like nausea, diarrhea, dyspepsia, flatulence and abdomen pain. This leads to poor patient compliance.

Inositol is a polyalcohol, a physiological compound of sugar family of which two stereoisomers are found in our body, myoinositol (MI) and D-chiro inositol (DCI). DCI is very scarce in diet and synthesized endogenously from MI by insulin dependent epimerase enzyme. [11]

D-chiroinositol is an important second messenger in insulin signal transduction. It acts as a precursor for inositol triphosphate (IP3) and phosphatidyl inositol 3 kinase (PI3K), needed for actions of insulin like increased glucose uptake, thus improving insulin sensitivity. [12, 13] Thus, DCI can be used as an alternative to metformin to improve insulin sensitivity. Certain studies have demonstrated the efficacy of DCI in reducing metabolic and endocrinological abnormalities in PCOS patients [14]. This study was undertaken to demonstrate the efficacy and safety of D-chiro inositol since limited studies are available in India regarding supplementation of inositol in PCOS.

REVIEW OF LITERATURE

EPIDEMIOLOGY

PCOS is the most common endocrine disorder of women of reproductive age group and affects approximately 4 – 15% of females worldwide and 2 – 25% in India. Among infertile women, about 20% infertility is attributed to anovulation caused by PCOS [1]

HISTORY OF PCOS

PCOS was previously called **Stein-Leventhal Syndrome**, named after the two North American gynecologists, Stein and Leventhal who first described it. They worked on patients who had obesity, hirsutism, irregular menstrual cycles and had bilateral, large ovaries with multiple cysts. They performed ovarian biopsy by taking out wedges of tissue. Surprisingly, those women resumed regular menstrual cycles after few months of biopsy. [4, 15]

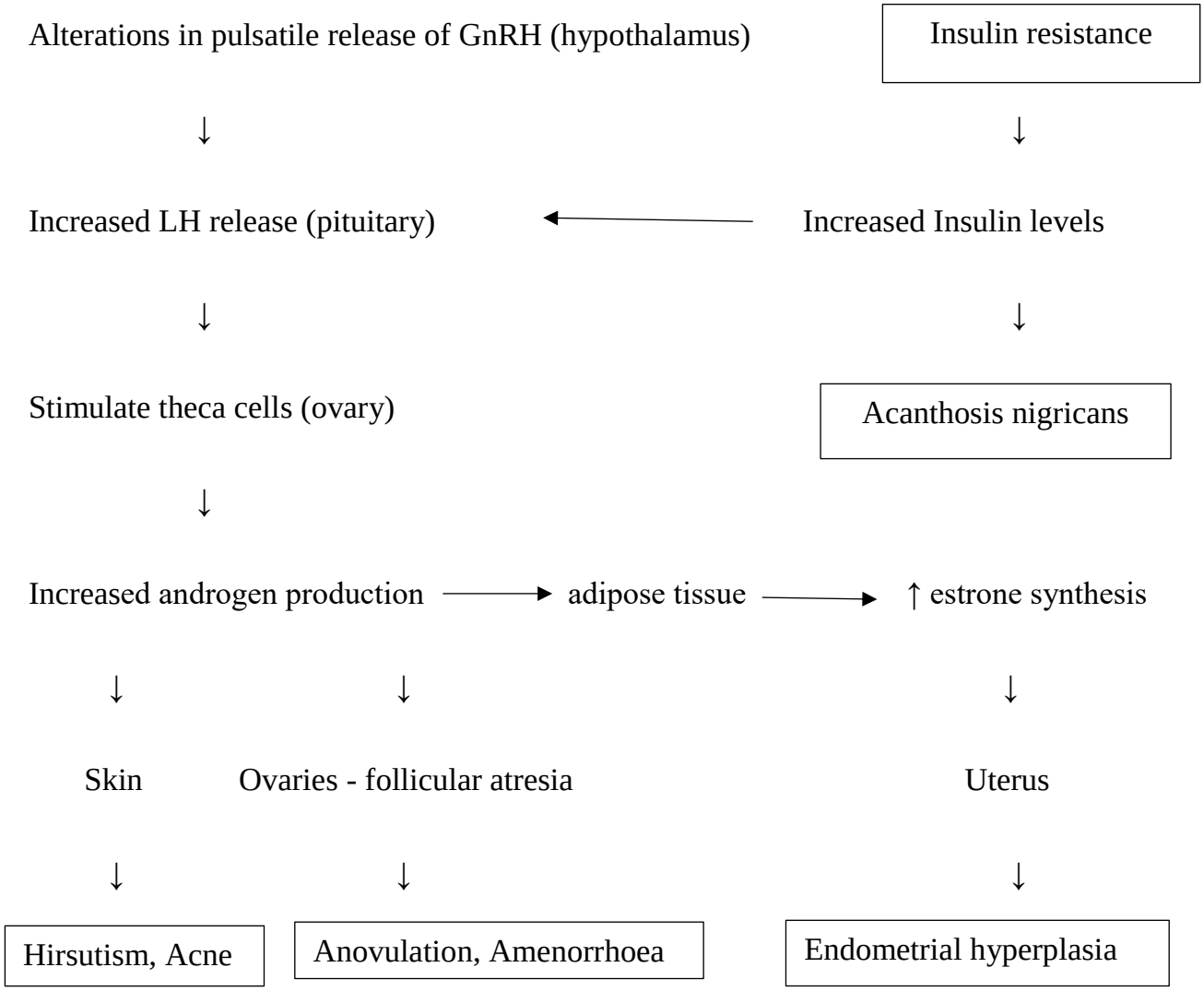
Based on this work, primary defect in ovary was considered to be responsible and was referred to as Polycystic Ovarian Disease (PCOD). However, after extensive work, PCOD is no longer a disorder confined to ovary, but involves a complex pathophysiology of multiple organs like hypothalamus, pituitary, adrenals and adipose tissue. Hence, PCOD is now referred to as **Polycystic Ovary Syndrome (PCOS).** [16]

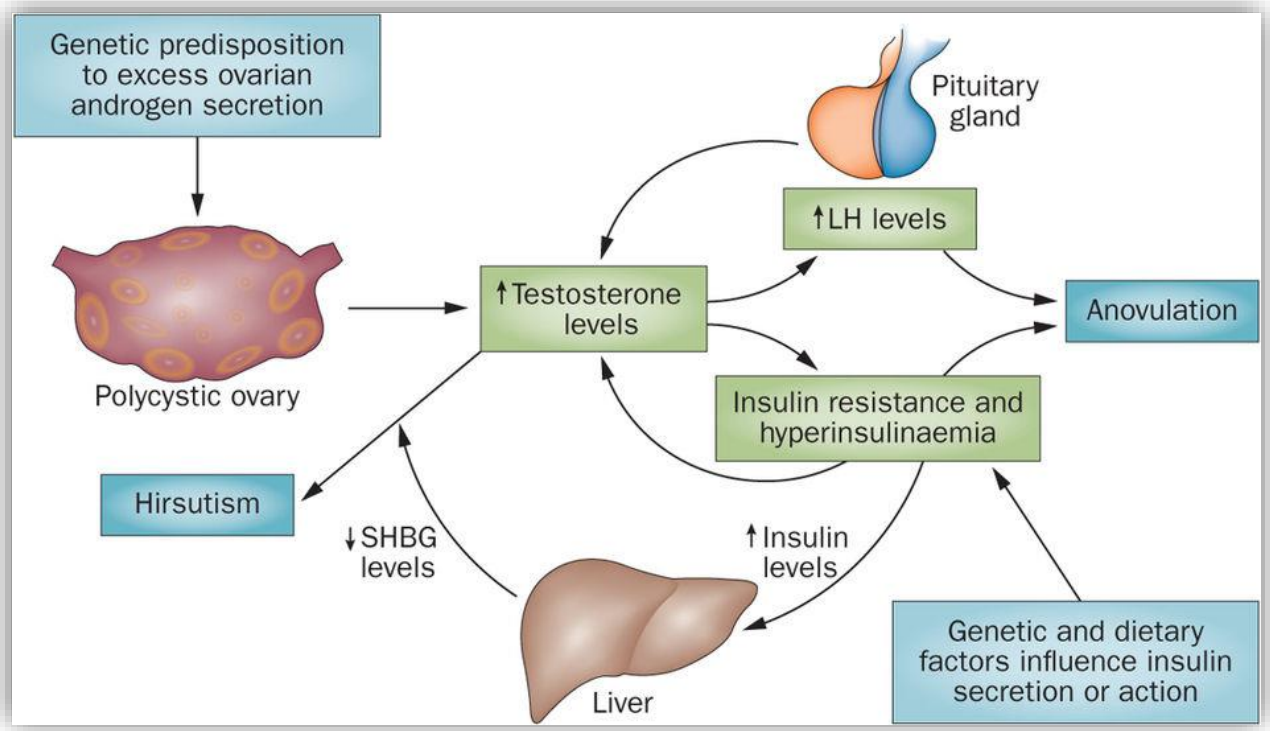
ETIOLOGY

The underlying etiology of PCOS is not exactly known. PCOS is a complex heterogenous disorder and is attributed to various causes like familial, genetic and environmental factors. Familial occurrence is noted among siblings (sisters) and offspring (female child). Environmental factors like stress, life style changes including increased fat and carbohydrate diet and reduced physical activity. [1, 2]

Genetic factors include CYP 21A1 gene mutation with Autosomal dominant and X-linked dominant mode of inheritance. Invitro studies of ovarian theca lutein cells suggest that PCOS is associated with dysregulation of CYP11A1 gene. This gene encodes for cholesterol cleaving enzyme, which is the rate limiting step in steroid synthesis. Also, upregulation of genes coding for enzymes in androgen synthesis and gene for insulin receptor on chromosome 19 may be involved. [1,17]

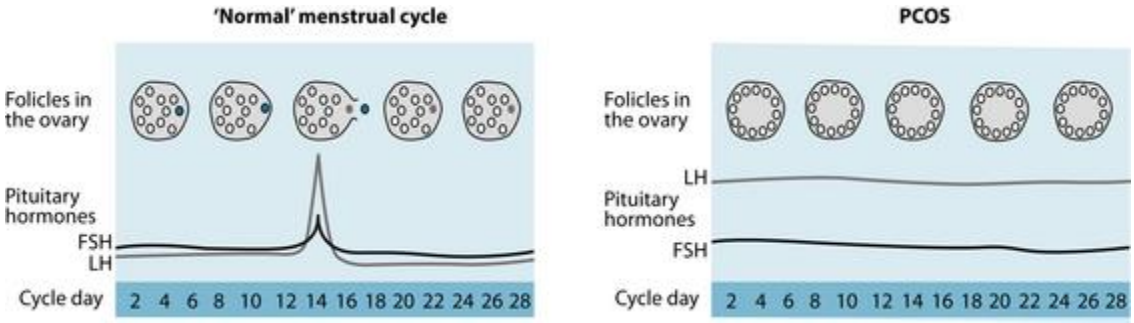
PATHOPHYSIOLOGY





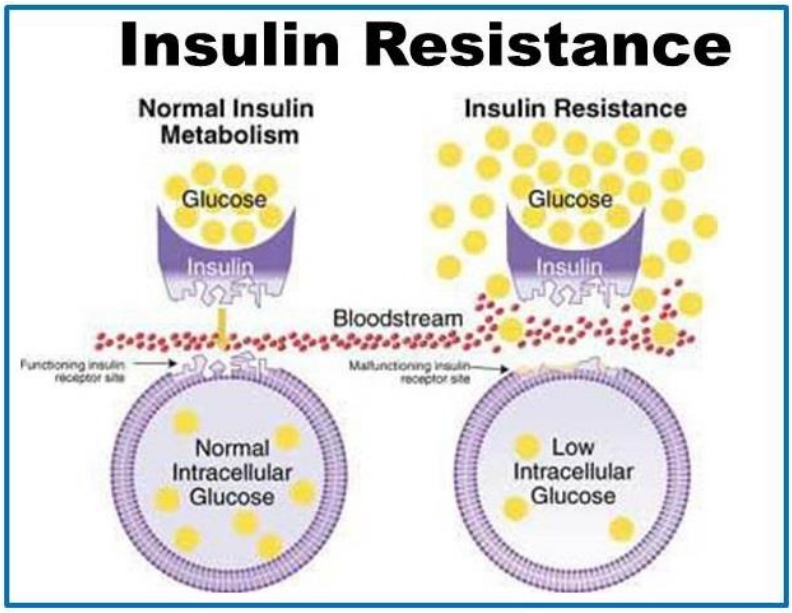
GONADOTROPINS:

- Anovulation in PCOS is due to inappropriate gonadotropin secretion. Alterations in pulsatile release of Gonadotropin Releasing Hormone (GnRH) leads to preferential production of luteinizing hormone (LH) compared to follicle stimulating hormone (FSH). [1] It may be due to hypothalamic dysfunction or abnormality in steroid feedback mechanism. In almost 50-60% patients, serum LH levels are high from onset of menstrual phase and LH:FSH ratio is 2:1 or even 3:1[4]

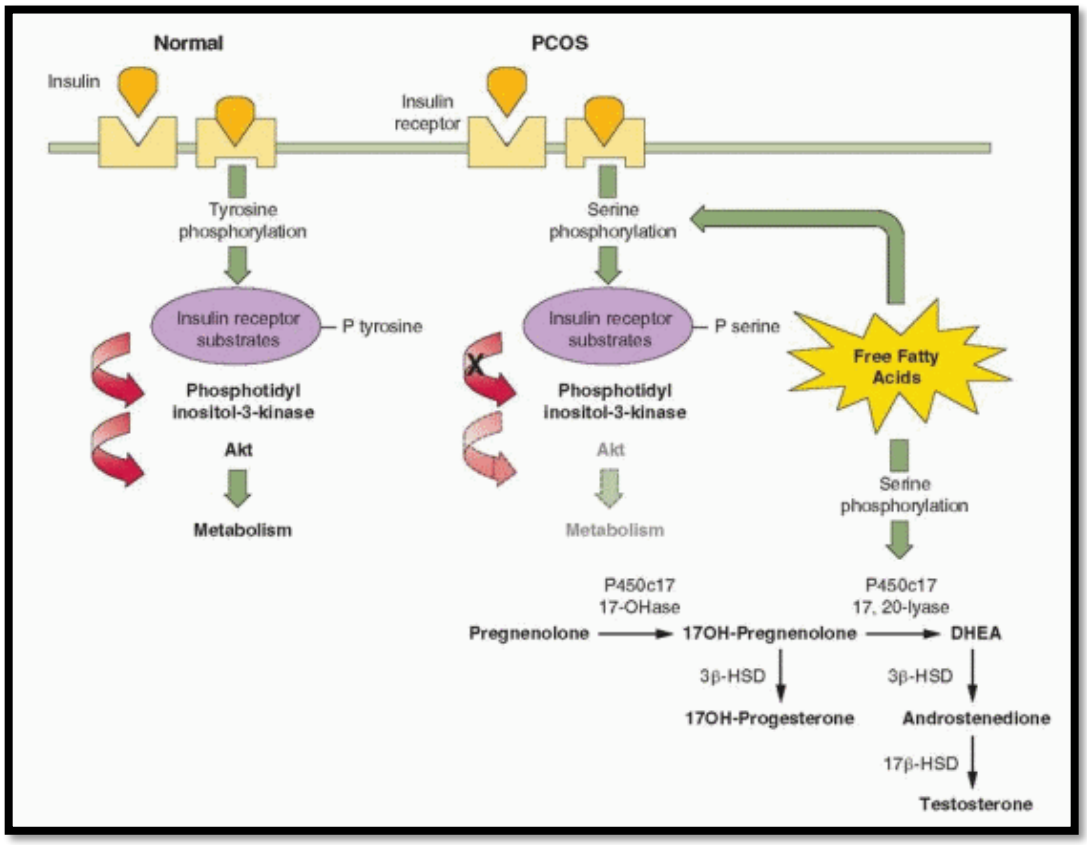


INSULIN RESISTANCE:

- Nearly 60-70% of women with PCOS have insulin resistance (IR)
- IR is defined as diminished ability of cells to respond to the action of insulin in transporting glucose from blood stream into muscle and other tissues. [18]



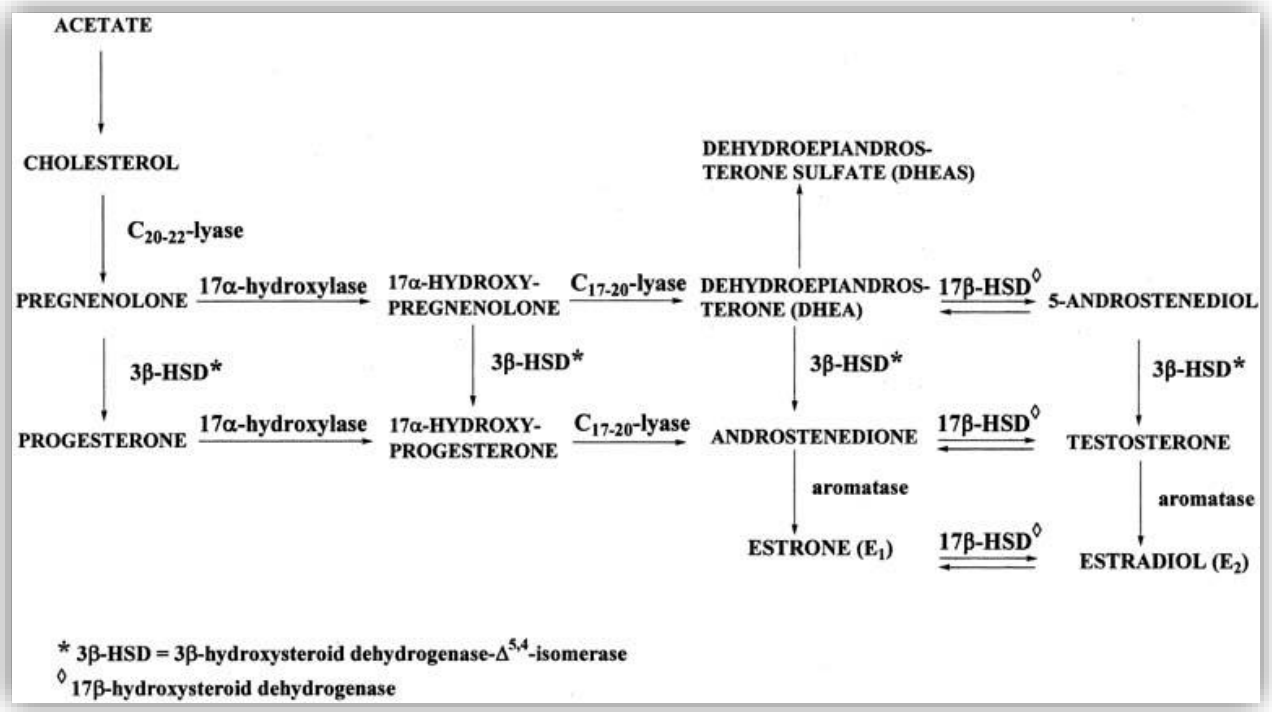
- Mechanism of reduced insulin sensitivity is due to postbinding abnormality in insulin receptor mediated signal transduction [19]
- Normally, when insulin binds to its receptor, there is activation of tyrosine kinase enzyme and phosphorylation of tyrosine residues of the receptor and IRS- insulin receptor substrates and further downstream of events occurs and this leads to actions of insulin. [20]
- In PCOS, there is phosphorylation of serine residues, hence decreased insulin action or insulin resistance is seen.



- IR is seen in approximately 80% of obese PCOS women and 30 – 40% of lean women with PCOS. [11]
- IR is sensed by pancreas as insulin deficiency and leads to compensatory hyperinsulinemia.
- Insulin stimulates luteinizing hormone (LH) to produce more androgens from theca cells of ovary leading to hyperandrogenism.

HYPERANDROGENISM:

- Under influence of insulin, LH stimulates excess androgen synthesis from theca cells of ovary. They include, testosterone, androstenedione, dehydro epiandrosterone (DHEA), DHEA-sulphate.
- Insulin and insulin like growth factor (IGF-1) along with LH , stimulate the activity of ovarian enzyme complex CYP 450c 17α , includes 2 enzymes – 17 α hydroxylase and 17-10 lyase which is needed for androgen synthesis in ovaries. [9]
- Increased androstenedione levels lead to increased estrone levels, due to peripheral conversion of androgens to estrogens by aromatase enzyme



- Insulin inhibits synthesis of SHBG – sex hormone binding globulin. (This is a glycoprotein synthesized from liver and binds to almost 99% of sex hormones normally.)
- This leads to increased free androgen levels and features of hyperandrogenism like acne, hirsutism, androgenic alopecia are seen.

HIRSUTISM

- Prevalence is 60 – 70% of PCOS women. [13]
- Within a hair follicle, testosterone is converted into DHT-dihydro testosterone by 5α reductase

- This converts soft, vellus hair to coarse terminal hair, in androgen sensitive areas, like, chin, upperlip, side of cheeks, chest, linea alba in lower abdomen. [1]
- Assessed by modified Ferriman-Gallwey scoring system [14]

ACNE:

- Prevalence is 30 – 40% in women with PCOS . [13]
- Hyperandrogenism leads to increased production of sebum in sebaceous glands. This along with hyperkeratosis leads to blockade of follicular opening and proliferation of Propionibacterium acnes and finally inflammation leads to scarring. [1]

ALOPECIA:

- Due to increased DHT levels in hair follicles.
- Features of progressive hair loss, either as recession in bitemporal areas or diffuse thinning at the crown with preservation of frontal hairline.

HYPERINSULINEMIA & HYPERANDROGENISM:

This association dates back to the bearded diabetic women reported by Archard and Thiers in 1921

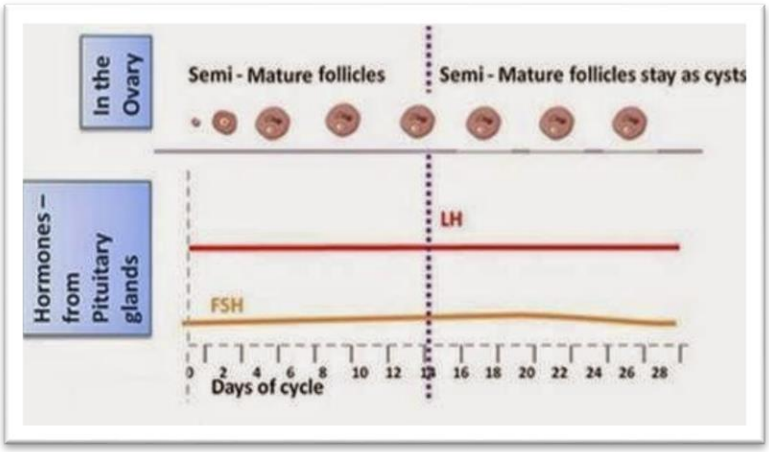
- Acanthosis nigricans is marker of insulin resistance

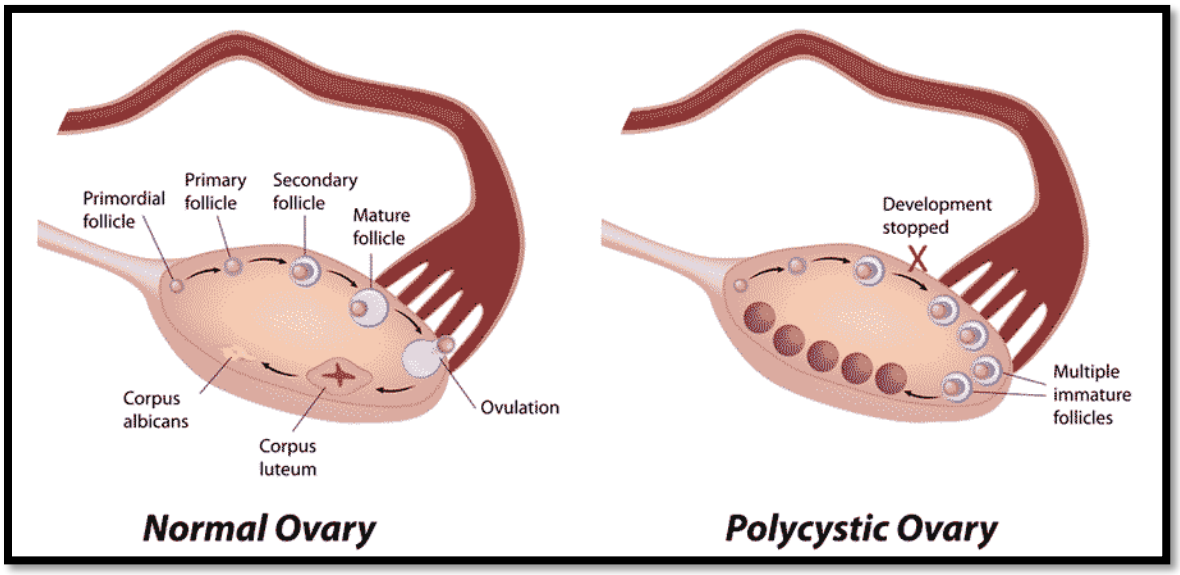
- IR is associated with **ACANTHOSIS NIGRICANS**, a condition with grey-brown velvety discoloration of skin in nape of neck, axilla, groin and under breasts.
- **HAIRAN syndrome** is Hyperandrogenism Insulin Resistance Acanthosis nigricans
- IR is associated with many disorders like DM, HT, CV diseases, obesity and dyslipidemia
- Therefore, PCOS is not a disease of short term consequences, but has long term health sequelae.
- IR is associated with obesity. IR with abdominal obesity leads to increased incidence of type 2 DM in later life
- Hyperinsulinemia is associated with increased levels of PAI-1 , plasminogen activator inhibitor type -1, which is associated with risk of CAD [8,9]
- Therefore, insulin lowering drugs help to reduce insulin levels, improve insulin sensitivity, reduce LH and androgen levels and restore ovulation.

ANOVULATION

- Hypersecretion of LH leads to menstrual irregularity

- Increased androgens cause atresia of follicles and failure of development of dominant Graafian follicle and absence of LH surge leads to anovulation. This causes reduced progesterone synthesis. [4]





- PCOS women have increased androgen, estrogen levels but low progesterone levels
- Women usually have irregular, infrequent cycles. Some women may have irregular, heavy bleeding. This occurs due to anovulation, absent progesterone synthesis and unopposed estrogen leading to endometrial hyperplasia, and heavy bleeding.

METABOLIC ABNORMALITIES

Women with PCOS develop complications such as type 2 diabetes, hypertension, cardiovascular diseases, endometrial carcinoma, in later life.

PCOS - DIAGNOSTIC CRITERIA: [1, 2]

ESHRE/ASRM (Rotterdam) 2003

(ASRM – American society for reproductive medicine

ESHRE – European society of human reproduction and embryology)

To include any two out of following three:

1) Oligo-ovulation or anovulation
2) Clinical and/or biochemical features of hyperandrogenism
3) Polycystic ovaries – in ultrasound

   With exclusion of any other endocrine abnormalities

AES- ANDROGEN EXCESS SOCIETY 2006

To include all of the following:

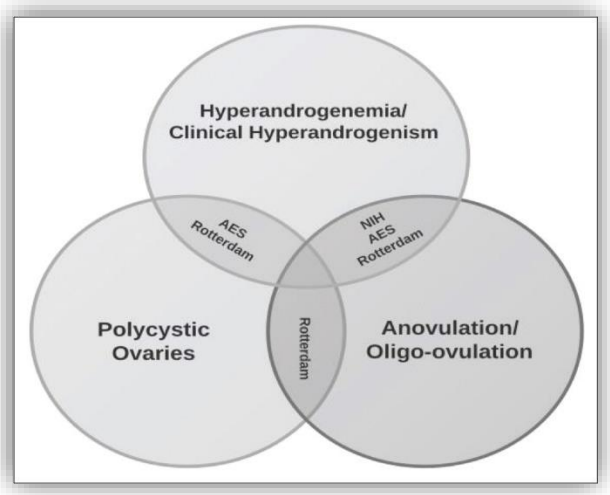
1) Hyperandrogenism : hirsutism and/or hyperandrogenemia
2) Ovarian dysfunction : oligo-anovulation and/or polycystic ovaries
3) Exclusion of other androgen excess or related disorders

NIH – NATIONAL INSTITUTE OF HEALTH 1990

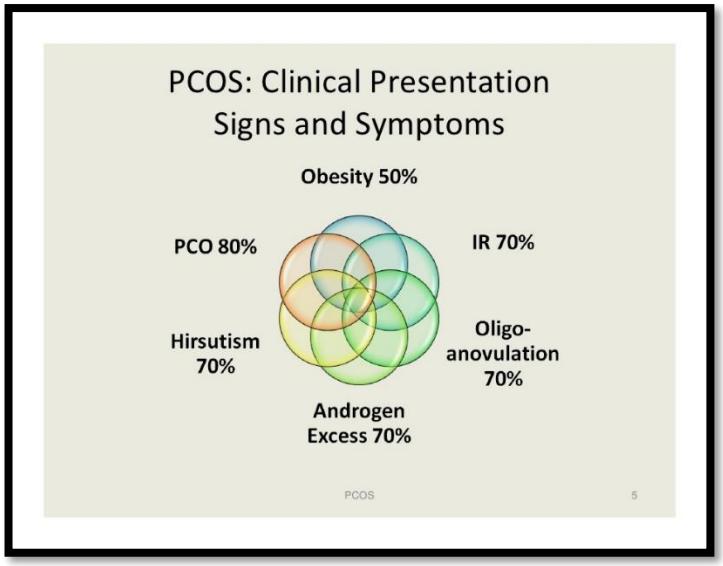
To include both of the following

1) Oligo-ovulation
2) Hyperandrogenism and/or hyperandrogenemia

   (with exclusion of related disorders)



PCOS -CLINICAL FEATURES



1) **MENSTRUAL DYSFUNCTION**:

- May range from amenorrhea to oligomenorrhea to menometrorrhagia.. these features begin with menarche itself.
- Amenorrhea is absent cycles for >= 3 consecutive months.
- Oligomenorrhea is less than 8 cycles in one year.

2) HYPERANDROGENISM:

- Clinically manifests as acne, hirsutism and androgenic alopecia (male type baldness)
- If features of virilization also seen, rule out androgen secreting tumors of ovary/ adrenal gland

HIRSUTISM:

- It is defined as coarse, dark, terminal hairs distributed in male pattern in a female.

- Seen in androgen sensitive areas, like, chin, upperlip, side of cheeks, chest, linea alba, lower abdomen.
- Assessed by modified Ferriman-Gallwey scoring system [21]

SCORE	HIRSUTISM
< 8	No hirsutism
9 – 16	Mild hirsutism
17 – 25	Moderate hirsutism
>25	Severe hirsutism

Score more than 8 is considered as having hirsutism

ACNE:

- In face and upper back
- As comedons, nodules and heals by scarring

ALOPECIA:

- Male type baldness is noted in bitemporal areas of scalp

METABOLIC ABNORMALITIES: [9]

INSULIN RESISTANCE:

- 50-70% of women with PCOS have insulin resistance

- Leads to compensatory hyperinsulinemia, which helps to maintain euglycemia
- IR is seen in both lean and obese PCOS women [14]

METABOLIC SYNDROME: [10]

SL.NO	RISK FACTOR	CRITERIA
1	Waist circumference	>88cm or 35 inches
2	Serum triglyceride	>150mg/dl
3	Serum HDL	<50 mg/dl in female
4	Blood pressure	>140/90 mg/dl
5	Fasting blood glucose	>100 mg/dl

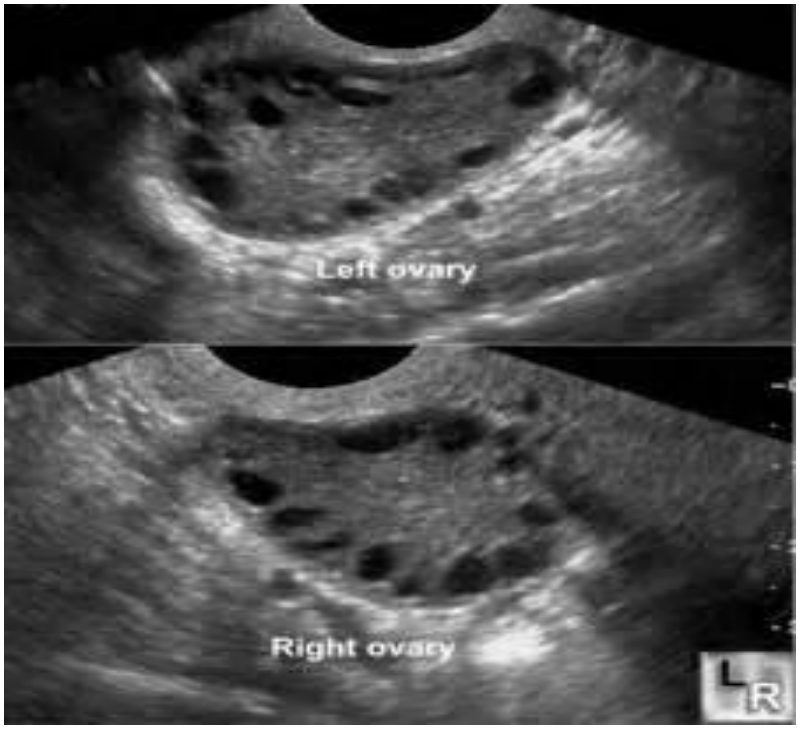
MANAGEMENT OF PCOS

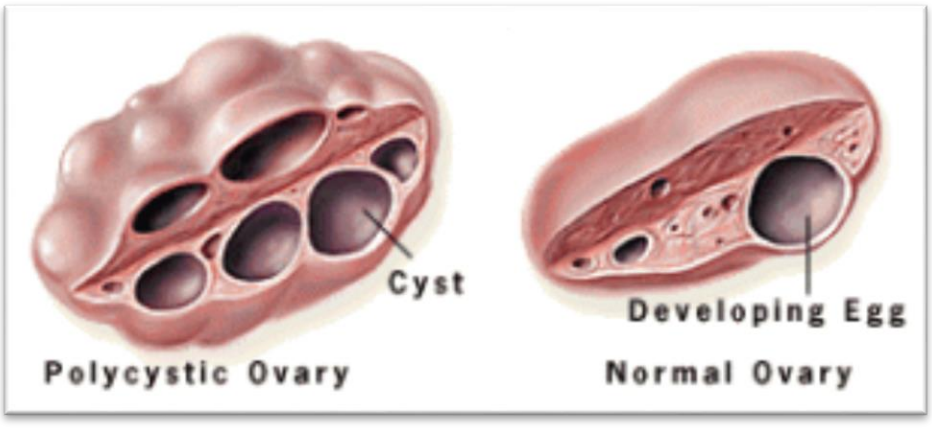
INVESTIGATIONS: [2]

PARAMETER	PCOS	NORMAL RANGE
FSH (day 3)	Normal	4 – 8 mIU/ml
LH (day 3)	>10 mIU/ml, increased	4 – 8 mIU/ml
FS/LH ratio	1:2 or 1:3	1:1
Free testosterone	Increased	0.6 – 6.6 pg/ml
Androstenedione	Increased	50 – 250 ng/dl
Dehydroepiandrosterone (DHEA)	Increased	130 – 980 ng/dl
Sex hormone binding globulin (SHBG)	Decreased	18 – 114 nmol/L
Estrone E2	Increased	1.5 – 20 pg/ml
Fasting glucose	Increased	70 – 100 mg/dl
Fasting insulin	>10 µIU/ml, Increased	3 – 8 µIU/ml
Fasting cholesterol	Increased	< 200mg/dl

ULTRASONOGRAM ABDOMEN AND PELVIS:

Both ovaries have multiple follicles in the periphery giving necklace pattern.





HOMA-IR index

- HOmeostasis Model Assessment.
- Measurement of Insulin resistance.
- HOMA – IR = $\frac{\text{Fasting glucose} \times \text{Fasting insulin}}{405}$

HOMA score: Normal < 3

Moderate Insulin resistance : 3 – 5

Severe Insulin resistance : > 5

MANAGEMENT

WEIGHT REDUCTION

- Weight loss helps to improve insulin sensitivity, increase SHBG concentration, reduce free testosterone levels
- Modest weight reduction of 5 – 10% helps to restore ovulation and menstruation
- Thessaloniki ESHRE/ASRM workshop recommended weight loss as 1st line therapy in obese PCOS women willing for conception. [1]

LIFESTYLE CHANGES:

- This includes dietary habits and increase in physical activity.
- Take diet rich in fiber and complex carbohydrates and avoid simple sugars

- Avoid saturated fat and use poly unsaturated fatty acids and Omega 3 fatty acid containing oil
- Take as small, frequent meals
- Reduce alcohol intake, avoid smoking.

DRUGS TO IMPROVE INSULIN SENSITIVITY

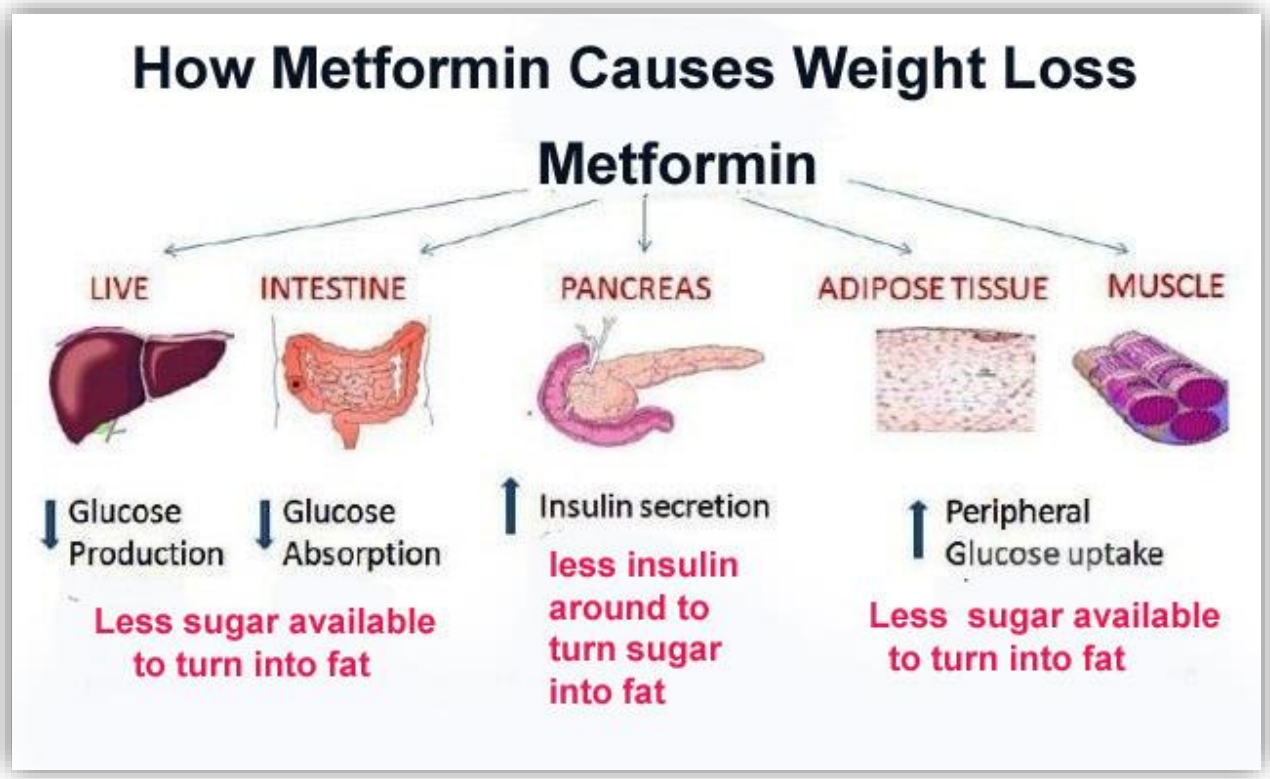
1) **METFORMIN**:

   It is a Biguanide

MECHANISM OF ACTION:

- activation of AMP dependent protein kinase (AMPK) [3]
- This interferes with mitochondrial respiratory chain, leading to anaerobic glycolysis and reduced ATP synthesis
- Reduced intracellular ATP levels leads to increased glucose uptake by muscles and thus, increased peripheral utilization of glucose
- Reduces hepatic glucose output
- Reduces intestinal glucose uptake
- Reduces substrate for gluconeogenesis by inhibiting lipolysis
- Reduces LDL, TG and slight increase in HDL. [3, 4]

- Metformin is used for PCOS, improves insulin sensitivity by increasing insulin stimulated release of D-chiro inositol containing inositol phosphoglycan mediators in women with PCOS.



PHARMACOKINETICS:

- Good oral absorption, not plasma protein bound, not metabolized in liver and excreted unchanged in urine.

- OCT 1 (organic cation transporter) helps in MF uptake into hepatocytes and myocytes
- OCT 2 helps in drug uptake into proximal tubules of kidney and active secretion in urine
- Ideal dose is 500mg or 1000mg BD
- Start with low dose and then titrate upto a maximum of 2000-2500mg over several weeks

ADVERSE EFFECTS:

- GIT disturbances (10-20%) - nausea, diarrhea, metallic taste, dyspepsia, anorexia, abdominal bloating.
- Rarely, lactic acidosis: 3–6 per 1,00,000 patients
- When taken alone, doesn't cause hypoglycemia (since doesn't increase insulin levels, only increases sensitivity)

CONTRAINDICATIONS:

Renal failure, hepatic failure, congestive heart failure, respiratory failure alcoholics

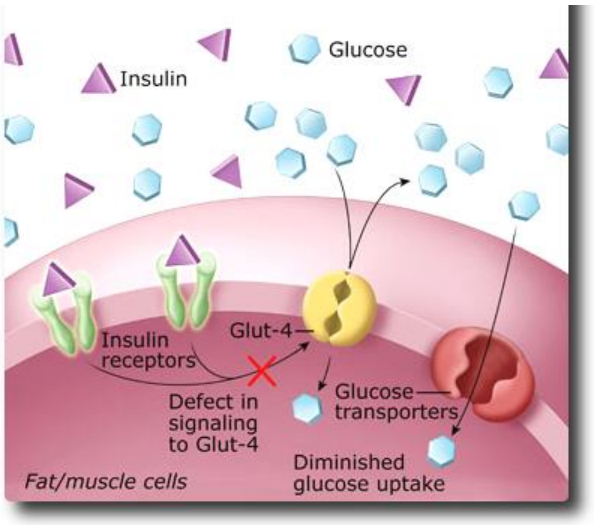
Pregnancy : category B drug.

THIAZOLIDINEDIONES:

MECHANISM OF ACTION

- Acts by increasing insulin sensitivity in muscles
- In adipose tissue – acts on nuclear receptor - PPAR γ peroxisome proliferator activated receptor γ and regulates gene expression that may be activation or repression.
- Helps in translocation of GLUT 4 receptors from intracytoplasmic vesicles to cell membrane, thus facilitates blood glucose entry into cells in muscle and adipocytes and helps to improve insulin sensitivity.

INSULIN RESISTANCE



- In adipocytes, it helps in adipocyte proliferation, differentiation, fatty acid uptake and storage. By promoting storage of fat in adipose tissue, TZD help to improve insulin sensitivity.

- Only drug available is PIOGLITAZONE
- Dose 15- 45 mg OD
- But rarely used for insulin resistance in PCOS.

Adverse effects:

- Weight gain due to fluid retention and edema.
- Hepatotoxicity, but rare
- Increased risk of heart failure – due to fluid retention
- Increased risk of fractures – preferential differentiation of mesenchymal stem cells into adipocytes and not into osteocytes, leading to weak bones
- Contraindications:

  Heart failure, liver failure, pregnancy and lactation [3,6]

DRUGS TO REDUCE ANDROGEN LEVELS

1) ORAL CONTRACEPTIVES:

Mechanism: Combined oral contraceptives containing estrogen and progesterone suppress LH production by negative feedback inhibition, thus reduce androgen synthesis.

- ethinyl estradiol (EE) with desogestrel (estrogen with pure progestin)

- combined pills with anti androgenic effect : ethinyl estradiol with cyproterone acetate

- EE with drospirenone (spironolactone derivative with anti androgenic activity)

2) ANTI ANDROGENS

- Drugs that prevent further hair growth and no effect on pre-existing hairs
- Depilatory cream : Eflornithine or mechanical by electrolysis

3) ANTI ANDROGENS WITH COMBINED OC PILLS

- FLUTAMIDE: androgen receptor antagonist, inhibits binding of testosterone and DHT to androgen receptor.
- FINASTERIDE: 5 α reductase inhibitor, prevents conversion of testosterone to active form, dihydro testosterone (DHT) .
- SPIRONOLACTONE: aldosterone antagonist and anti androgen property.
- CYPROTERONE ACETATE: synthetic progestin with anti androgenic property

DRUGS TO PREVENT ENDOMETRIAL HYPERPLASIA

In anovulation, persistent elevation of estrogen in absence of progesterone leads to endometrial hyperplasia and malignancy

Drug - Progesterone in 2nd half of cycle – medroxyprogesterone acetate 5 - 10mg/ day for 10 days, every month

Mechanism – helps in shedding of endometrium, built up by estrogen and induces regular, withdrawal bleeding

MANAGEMENT IN ADOLESCENT GIRLS

Irregular, infrequent cycles for> 2 years following menarche

1) Obesity – life style modifications (diet and exercise)
2) Acne, hirsutism – mechanical hair removal with combined oral pills containing cyproterone + ethinyl estradiol.
3) If severe hirsutism – anti androgens (flutamide/ finasteride)
4) With 2' amenorrhea / infrequent cycles – medroxyprogesterone for last 10 days of cycle
5) With impaired glucose tolerance or features of insulin resistance or family history of type 2 DM – METFORMIN (to prevent metabolic syndrome in later life)

MANAGEMENT OF INFERTILITY

1) First line of therapy is weight loss
2) Ovulation induction by CLOMIPHENE CITRATE

   SERM / Anti estrogen

   Mechanism: estrogen receptor antagonist in hypothalamus, thus blocks feedback inhibition of estrogen and increases release of GnRH and gonadotrophins.

   Dose : 50 -150mg / day for 5 days, given from day3 of cycle.

   Maximum upto 6 months and never more than 12 months of therapy

   Clomiphene resistance is seen in around 15 – 30% of cases

   Adverse effects: multiple pregnancy, ovarian enlargement and hyperstimulation, hot flushes and weight gain.

3) If clomiphene fails – aromatase inhibitors:

   Mechanism: Prevent conversion of androgens to estrogens in peripheral tissues

   This reduces estrogen levels, thus negative feedback inhibition of E on FSH is removed. Increased FSH helps in follicular development and maturation and thus, induces ovulation

   LETROZOLE – 2.5mg/day from day 3 for 5 days

4) METFORMIN:

   Indicated mainly in impaired glucose tolerance (IGT) and BMI > 35 kg/m^2

5) GLUCOCORTICOIDS

   Dexamethasone 0.5mg/day from day 3 for 10 days, adjuvant to combined OC pills

6) GnRH agonist:

   Helps to reduce LH and thus, reduces androgen levels.

7) If ovulation induction is failed by above methods,

   a) Gonadotrophins (human chorionic gonadotrophin/ human menopausal gonadotrophin) with IVF invitro fertilization

   b) Laprascopic ovarian drilling (LOD) – multiple holes are made in ovary using cautery, which destroys ovarian stroma which produces excess androgens.

DRUG TREATMENT FOR MORBID OBESITY:

1) SIBUTRAMINE :

   - Inhibits reuptake of monoamines like DA, NE, 5-HT and enhances satiety

2) ORLISTAT:

- Pancreatic and gastric lipase inhibitor
- Helps to reduce digestion and absorption of fat from intestine.

BARIATRIC SURGERY:

Patients with morbid obesity (BMI > 40) who do not respond to diet, lifestyle modifications and drugs.

DRAWBACKS OF EXISTING MEDICATION

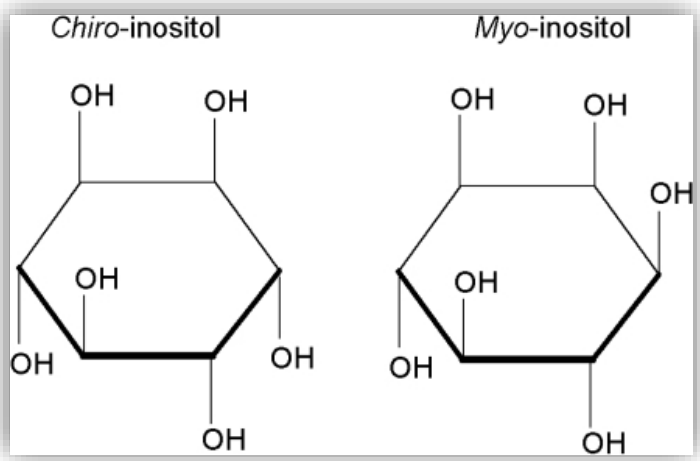
1) METFORMIN – causes gastrointestinal effects like nausea, diarrhea, dyspepsia, flatulence, etc. This reduces the compliance of patients. Also many contraindications and drug interactions are present.
2) ORAL CONTRACEPTIVES – Combined pills containing estrogen and progesterone. There is increased risk of thromboembolic events, breast tenderness, alteration in lipid levels
3) CLOMIPHENE CITRATE – can cause high parity, hot flushes, hyper stimulation of ovaries (OHSS)
4) ANTI ANDROGENS – SPIRONOLACTONE – can cause hyperkalemia, irregular menstrual cycles, GIT distress, hepatitis, abnormality in sexual differentiation of male fetus.

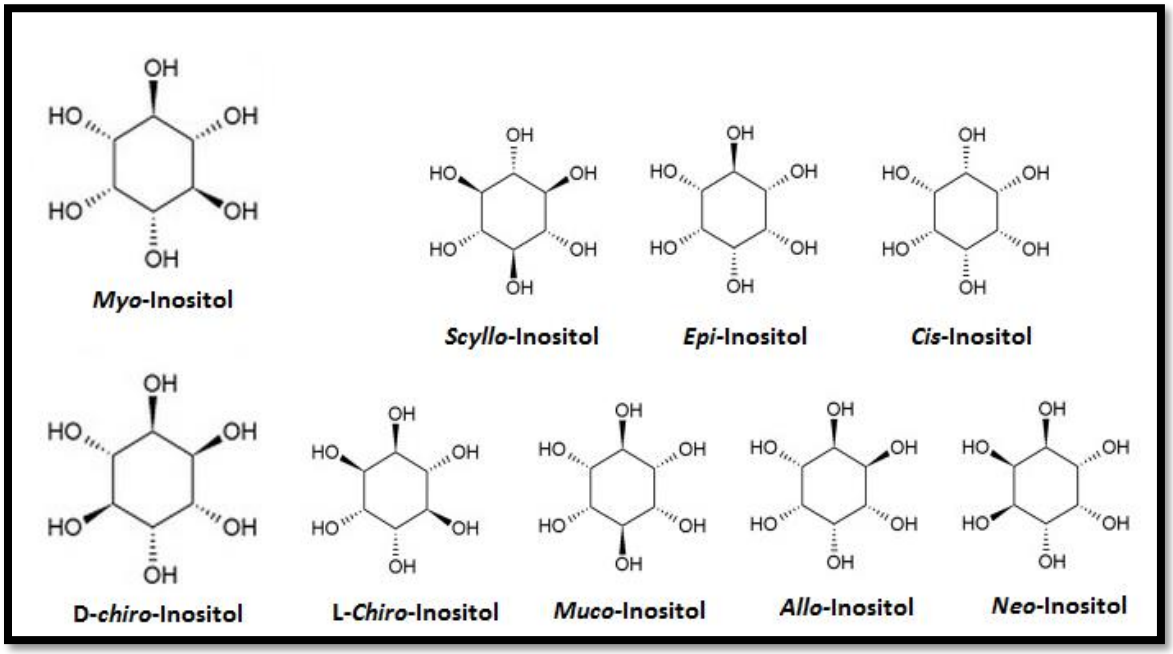
Current treatment for PCOS is life style modifications, oral contraceptives for menstrual cycle regularity, anti androgens for hyperandrogenism, metformin for metabolic complications and clomiphene for ovulation induction. All these help to alleviate individuals components of PCOS. The above medications have certain disadvantages. These can limit the clinical outcome of such medications. But DCI acting as second messenger of insulin signaling pathway, helps to the reduce correct the basic pathogenesis of insulin resistance and this inturn helps to reduce serum insulin, LH, androgen levels and regulate menstrual cycle, thereby improve ovulation and fertility. Also the drug has an excellent safety profile. Hence, keeping these in mind, D-chiro inositol appears to be a promising therapy.

INOSITOL – DRUG INFORMATION

CHEMISTRY & STRUCTURE:

In 1850, Johanes Joseph Scherer isolated a compound from muscle and named it as INOSITOL. In Greek, *in* means – fiber, *ose* – carbohydrate, *ite* – ester, *ol* – alcohol. It is a hexahydroxy-cyclohexane and has same molecular formula of glucose $C_6H_{12}O_6$. Inositol has 9 stereoisomers, of which Myo-inositol and D-chiro inositol are very important. [33] Both MI and DCI being stereoisomers have similar structure but differ in only one hydroxyl group. [34]


Chiro-inositol
Myo-inositol
OH


***Myo*-Inositol**
***Scyllo*-Inositol**
***Epi*-Inositol**
***Cis*-Inositol**
D-*chiro*-Inositol
L-*Chiro*-Inositol
***Muco*-Inositol**
***Allo*-Inositol**
***Neo*-Inositol**

SOURCE:

- Source of inositol is both endogenous production in body and also from diet, chiefly fruits, nuts, grains and beans.
- High levels of inositol were found in testis, seminal vesicles, prostate gland and ovaries [36,37]
- The seminal fluid in male and follicular fluid in female are the richest sources of inositol in the body. [38]
- DCI is very scarce in diet and so needs dietary supplement

EVIDENCE FOR SECOND MESSENGERS FOR INSULIN

Insulin has multiple effects on glucose metabolism in our body like activation of glucose transport into cells and glycogen synthesis in muscle and liver. But sometimes, these effects occur in discordance with each other. [39]

- In a study, when a rat heart was perfused with insulin, increased glucose transport was seen but glycogen synthesis was not activated. [40]

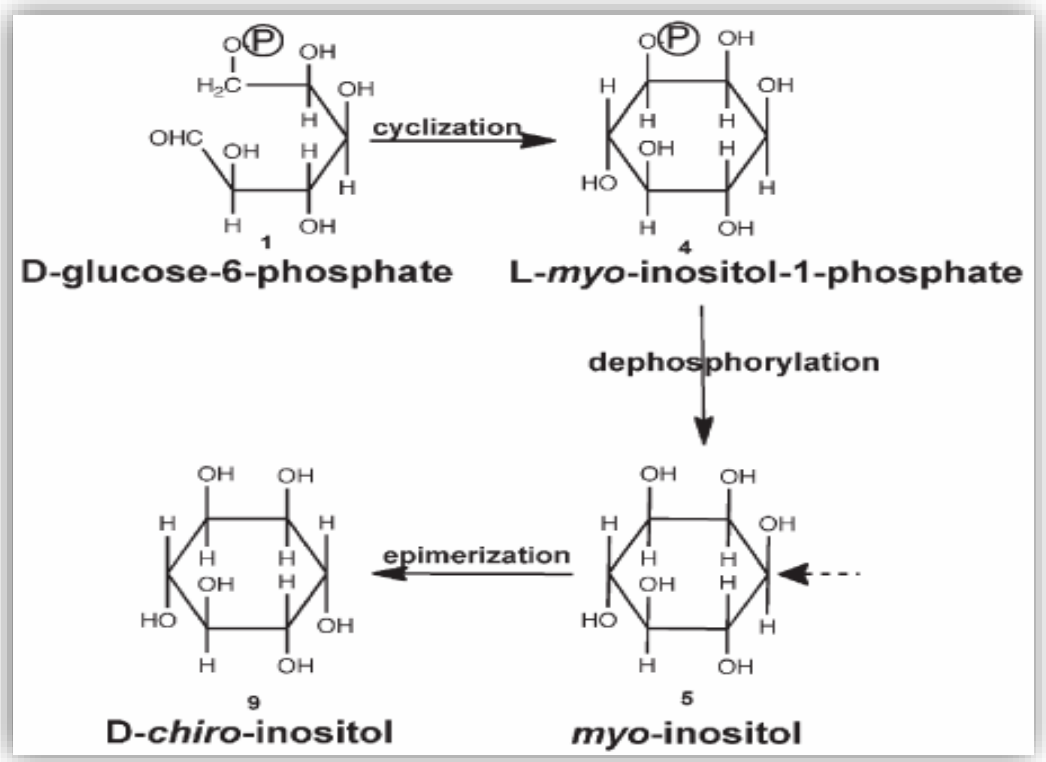
- When rat diaphragm was treated with N-ethylmaleimide, insulin activated glycogen synthesis was observed but no effect was seen in glucose uptake.[41]
- These studies suggest the possibility of more than one downstream event in insulin signaling pathway. This led to the identification of a cytoplasmic second messenger, inositol which mediates some actions of insulin while major actions occur through insulin receptor – tyrosine kinase mediated phosphorylation of insulin receptor substrates (IRS). These two pathways operate in parallel and together account for the whole effects of insulin in glucose metabolism. [42]

IDENTIFICATION OF INOSITOL GLYCANS AS SECOND MESSENGERS

Biochemical purifications from rat liver led to isolation of two factors. The first glycan contained D-chiroinositol plus galactosamine which activated pyruvate dehydrogenase phosphatase. The second glycan contained Myoinositol, galactose, glucosamine, and ethanolamine.[43,44] When injected in vivo, both glycans were insulin mimetic. On intravenous injection, they reduced blood glycose level in streptozocin (STZ) induced diabetes in rats. On intraperitoneal injection, they stimulated glucose deposition as glycogen into rat diaphragm muscles. [45]

SYNTHESIS:

Glucose 6 phosphate (G6P) is isomerised by inositol-3-phosphate synthase to myoinositol-1-phosphate, which gets dephosphorylated by phosphatase to myo inositol (MI). MI is converted into D-chiro inositol (DCI) by epimerase [35]

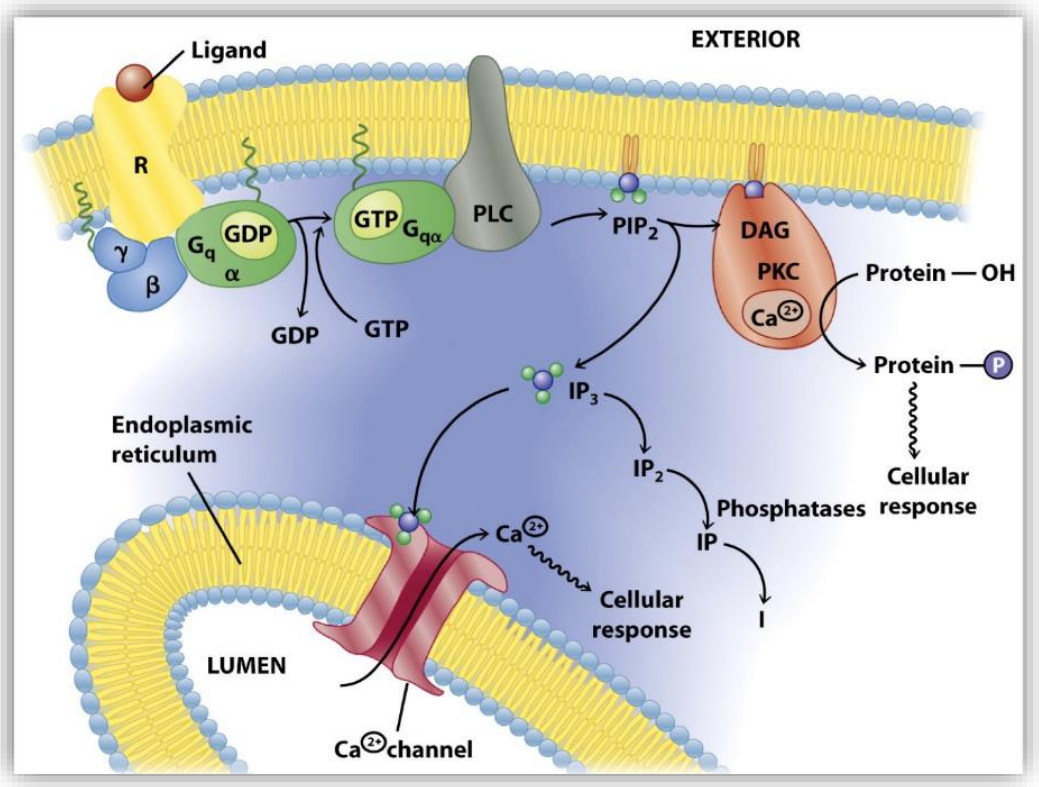


- Joseph Larner, demonstrated that MI is converted into DCI in vitro in fibroblasts and in vivo in rats, and this process is stimulated by insulin dependent epimerase enzyme [46].
- He showed that epimerase activity was reduced in cytoplasmic extracts of liver, muscle and adipose tissue from GK type 2 diabetic rats compared to

Wistar rats (control animals). This was due to insulin resistance and they had reduced DCI levels, compared to MI levels in those organs. [47]

PHYSIOLOGICAL ROLE

- Inositol is synthesized by both prokaryotes and eukaryotes cells. It gets incorporated into cell membranes as phophatidyl inositol (PI) and its phosphates like phosphtidyl inositol diphosphate (PIP2) which dissociates into IP3 and DAG. IP3 acts as second messenger regulating many hormones like insulin, Follicle stimulating hormone, and Thyroid stimulating hormone. [48]



- In 1988, Larner *et al* concluded that MI and DCI are the 2 stereoisomers, which function as chemical mediators of insulin, by acting through different mechanisms.[49]

INOSITOL AND INSULIN RESITANCE

- Impairment in insulin signaling could be due to defect in inositol phosphoglycan (IPG) second messenger pathway. [34, 50]
- Deficiency of this mediator is due to defect in epimerase enzyme needed for conversion of MI to DCI or due to excess catabolism of DCI before renal elimination. Thus, exogenous administration of DCI would help to replenish the extracellular stores and restore IPG content in insulin targeted tissues like skeletal muscle. [24, 25]
- In PCOS, a defect in tissue availability of inositol or IPGs mediators may contribute to insulin resistance. [19,51]
- IR leads to compensatory hyperinsulinemia and excess insulin stimulates LH which increases androgen production from theca cells of ovary and leads to hyperandrogenemia.
- This is the rationale for the suggested use of inositol in the management of insulin resistance syndromes, like impaired glucose tolerance, type 2 diabetes mellitus and polycystic ovary syndrome (PCOS).

CLINICAL STUDIES WITH INOSITOL

1) First clinical trial was in 1998, by Nestler *et al* which assessed the efficacy of DCI in PCOS, published in *The New England Journal of Medicine.* 44 obese PCOS women were divided into 2 groups receiving 1200mg DCI and placebo for 6-8 weeks. There was reduction in blood pressure, testosterone, triglyceride levels and ovulation occurred in 19 out of 22 women treated with DCI. [52]
2) DCI was given for obese PCOS women (BMI > 26kg/m^2) and found to reduce serum LH levels and testosterone and androstenedione levels and reduced BMI. Greater response was seen mainly in PCOS patients with diabetic relatives than without history of diabetes. [53]
3) DCI was found to regulate irregular menstrual cycles in PCOS women. This is done by reducing insulin resistance and reduction of AMH anti-mullerian hormone level. [54]
4) Another study was conducted in 68 patients with PCOS, treated with DCI 500mg BD or Metformin 850mg BD or placebo for 3 months, followed by ovulation induction. By reducing oxidative stress, DCI was found to improve maturity and quality of oocytes. [55]
5) All these studies are found to complement a Cochrane review, in which insulin sensitizers like metformin, pioglitazone and DCI were used for treatment in PCOS women. [56]

SAFETY OF DCI

Inositol is generally considered safe and but can cause gastrointestinal symptoms like nausea, vomiting. Mild headache due to hypoglycemia can occur very rarely. [57]

AIM & OBJECTIVES

AIM OF THE STUDY:

To evaluate the efficacy of D-Chiro inositol in women with polycystic ovary syndrome and to assess its safety and tolerability.

OBJECTIVES:

PRIMARY OBJECTIVE:

1) To assess the reduction in LH level.
2) To assess the regulation of menstrual cycle.

SECONDARY OBJECTIVE:

1) To assess the reduction in body weight, blood glucose and serum insulin levels.
2) To monitor any adverse effects with these drugs.

METHODOLOGY

METHODOLOGY

STUDY TYPE:

Interventional study.

STUDY DESIGN:

Randomized, open label, prospective and a comparative study.

STUDY CENTRE:

Institute of Pharmacology, Madras Medical College (MMC) in collaboration with Institute of Obstetrics and Gynecology, Rajiv Gandhi Government General Hospital (RGGGH), Chennai.

STUDY PERIOD :

The study was carried out from August 2016 to May 2017

STUDY DURATION:

12 weeks treatment period and 8 weeks follow up per patient.

STUDY POPULATION:

Women with Polycystic ovary disease attending Gynecology OPD, Institute of obstetrics and gynaecology, (IOG), Chennai.

SAMPLE SIZE:

Totally 60 patients.

20 patients – standard treatment (Metformin),

20 patients – study drug (D-chiroinositol (DCI).

20 patients – standard drug + study treatment (Metformin and DCI).

STUDY MEDICATION: Tab. D-Chiro inositol-600 mg BD,

Tab. Metformin 500mg TDS

INCLUSION CRITERIA

1. Women diagnosed with polycystic ovary syndrome, with menstrual irregularity.
2. Age 18 to 40 years.
3. Oligomenorrhoea (≤ 8menstrual cycles annually).
4. Hyperandrogenism (clinically and/or biochemically).
5. Patients willing to participate and give written informed consent .
6. Ability to comply with study procedure.

EXCLUSION CRITERIA

1. Patients with diabetes mellitus.
2. Patients with clinically significant cardiac, pulmonary, renal, hepatic, neurological, psychiatric illness and malignant disease.
3. Thyroid disorder or any other endocrine disorders. Eg; Hyperprolactinemia, adrenal disorders (CAH).
4. Ingestion of any investigational drug within 2 months prior to study enrolment.
5. Pregnancy and lactation.

STUDY PROCEDURE:

The study was conducted after obtaining permission from the Institutional Ethics Committee(IEC), and in accordance with the Declaration of Helsinki & Good Clinical Practice (GCP) guidelines.

Women with PCOS attending the Gynecology OPD, were explained about the study purpose and procedures. Written informed consent was obtained from the patients who were willing to participate in the trial.

SCREENING

All the patients were screened by demographic data, detailed medical history, clinical examination and laboratory investigations.

RECRUITMENT

Patients who fulfilled the inclusion and exclusion criteria were enrolled for the study.

RANDOMIZATION

The enrolled patients were randomized to Group A, Group B and Group C by simple randomization.

TREATMENT PLAN

Group A: (n=20) Tablet Metformin 500mg thrice daily for 12 weeks

Group B: (n=20) Tablet D-chiro inositol - 600mg once daily (wt < 60kg) and

600mg twice daily (wt > 60kg)

Group C: (n=20) Tablet Metformin 500mg twice daily with

Tablet D-chiro inositol 600mg once/twice daily according to the weight.

The study medication was issued for 2 weeks. After assessing the compliance of the patient at the end of 2 weeks, study medication was issued for the subsequent 2 weeks. The same procedure was followed till the completion of the study (12 weeks).

INVESTIGATIONS:

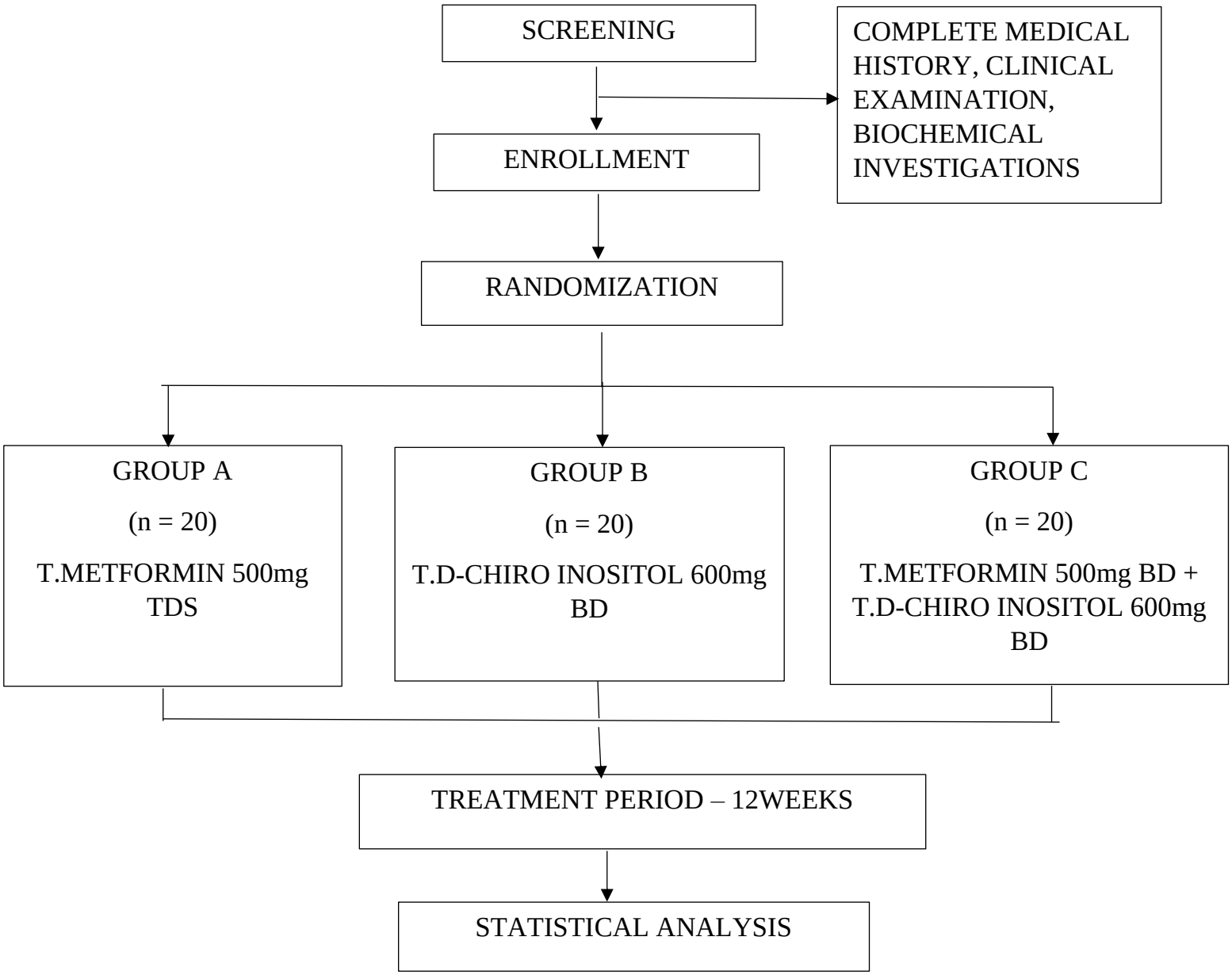
BASELINE INVESTIGATIONS

- Blood pressure.
- Body mass index
- Complete blood count
- Fasting and post prandial Blood sugar
- Fasting serum insulin level
- Fasting lipid profile: Serum Total Cholesterol, LDL, HDL & TGL

- Liver function test
- Renal function test
- Serum FSH, LH levels.
- Thyroid function test : TSH, free T3, free T4.
- Routine Urine Analysis.
- Chest X – ray
- Electrocardiogram
- Pelvic Ultrasonogram. (USG)

All the baseline investigations were done at the beginning and at the end of 12th week of the study.

STUDY FLOW CHART



STUDY VISITS

Screening and Baseline

1. Demographic details obtained

2. Complete medical history recorded

3. Vitals recorded and clinical examination performed

4. Enrollment was done

5. Written informed consent obtained

6. Laboratory investigations were done

- Complete blood count
- Lipid profile
- Blood Sugar
- Blood urea
- Serum Creatinine
- SGOT, SGPT
- Serum FSH, LH
- Serum fasting insulin
- Urine analysis
- ECG
- X ray chest PA view
- USG abdomen and pelvis

VISIT 1 (0 WEEKS)

1. Randomization of patient was done.

2. Physical & Clinical examination was done and BMI was calculated.

3. Vitals were recorded.

4. Drugs were issued for patients in all three groups.

5. Instructions given to return the empty bottle in the subsequent visit.

6. To report any adverse event if occurs.

VISIT 2 (2 WEEKS)

1. Received empty bottle.

2. Clinical examination was done and BMI was calculated.

3. Vitals were recorded.

4. Drugs were issued for the subsequent 2 weeks.

5. Instructions were given to return the empty bottle in the subsequent visit.

6. Adverse events if any, were recorded.

7. Patients were advised to report any adverse event.

VISIT 3 (4 WEEKS)

1. Received empty bottle.

2. Clinical examination was done and BMI was calculated.

3. Vitals were recorded.

4. Drugs issued for subsequent 2 weeks.

5. Instruction to return the empty bottle in the subsequent visit.

6. Adverse events if any, were recorded.

7. Patient advised to report any adverse event.

VISIT 4 (8 WEEKS)

1. Received empty bottle

2. Clinical examination was done and BMI calculated.

3. Vitals recorded

4. Drugs issued for subsequent 2 weeks

5. Instruction to return the empty bottle in the subsequent visit.

6. Adverse events if any, were recorded.

7. Patient advised to report any adverse event.

VISIT 5 (12 WEEKS)

1. Received empty bottle.

2. Clinical examination was done and BMI was calculated.

3. Vitals were recorded.

4. Adverse events if any, were recorded.

5. Laboratory investigation were done.

- Complete blood count
- Lipid profile
- Blood glucose, Blood urea, Serum Creatinine
- SGOT, SGPT
- Serum FSH, LH
- Fasting serum insulin
- Urine analysis

INSTRUCTIONS TO PATIENTS

The patients were instructed clearly about the regular intake of the medicines. They were also given proper advice to report for assessment and collection of drugs. They were counseled to report any adverse reactions if occurs.

COMPLIANCE

Patients' compliance was monitored by the empty bottle returned at each visit.

ADVERSE EVENTS

Any adverse event reported by the patient or observed by the physician during the study was recorded. The onset of adverse event, and its causal relationship to the study drug and the action taken for the adverse effect was recorded. Appropriate medical care was provided for the adverse event.

STATISTICAL ANALYSIS

The obtained data were analyzed statistically using SPSS software version 21. The biochemical parameters were analyzed statistically in all three groups. The differences within the groups before and after treatment were analyzed using student's paired t-test whereas the difference between three groups were analyzed using ANOVA. p value of < 0.05 is considered as statistically significant.

RESULTS

RESULTS

- This study was conducted to evaluate the effect of D-chiroinositol in comparison with metformin in polycystic ovary disease.
- Totally 108 patients were screened of which 60 patients were enrolled and completed the study.
- There were no drop outs in the study.

TABLE 1 – AGE DISTRIBUTION

AGE IN YEARS	GROUP A		GROUP B		GROUP C	
	NUMBER	%	NUMBER	%	NUMBER	%
< 20	4	20%	5	25%	4	20%
21 – 30	10	50%	11	55%	11	55%
31 – 40	6	30%	4	20%	5	25%
TOTAL	20	100%	20	100%	20	100%

Table 1 shows the age distribution of all three groups

Age group 21 - 30 years had more number of patients followed by age group 31 - 40 and < 20 years.

FIGURE 1 – AGE DISTRIBUTION

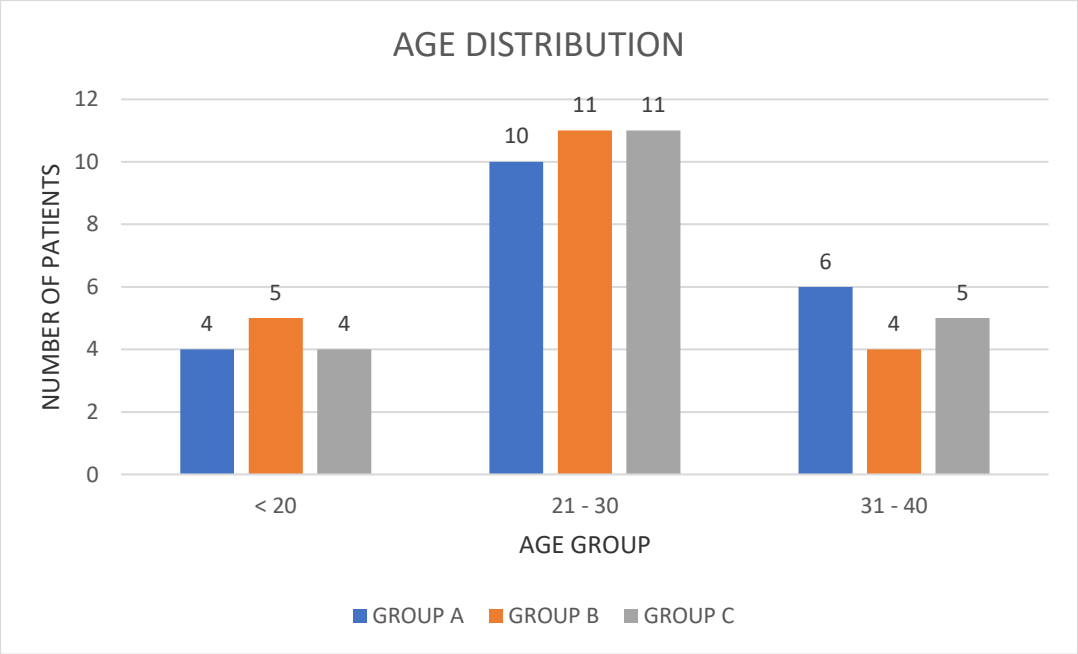


Figure 1 depicts age distribution in all three groups.

TABLE 2 – MEAN AGE DISTRIBUTION

GROUP	NUMBER OF PATIENTS	MEAN AGE (IN YEARS)	STD DEVIATION
GROUP A	20	26.35	6.89
GROUP B	20	25.65	6.30
GROUP C	20	26.20	5.92
P – VALUE	0.936		

Table 2 shows the mean age of all three groups.

- The mean age was similar in all three groups.
- There was no statistically significant difference between the groups.

FIGURE 2: MEAN AGE DISTRIBUTION

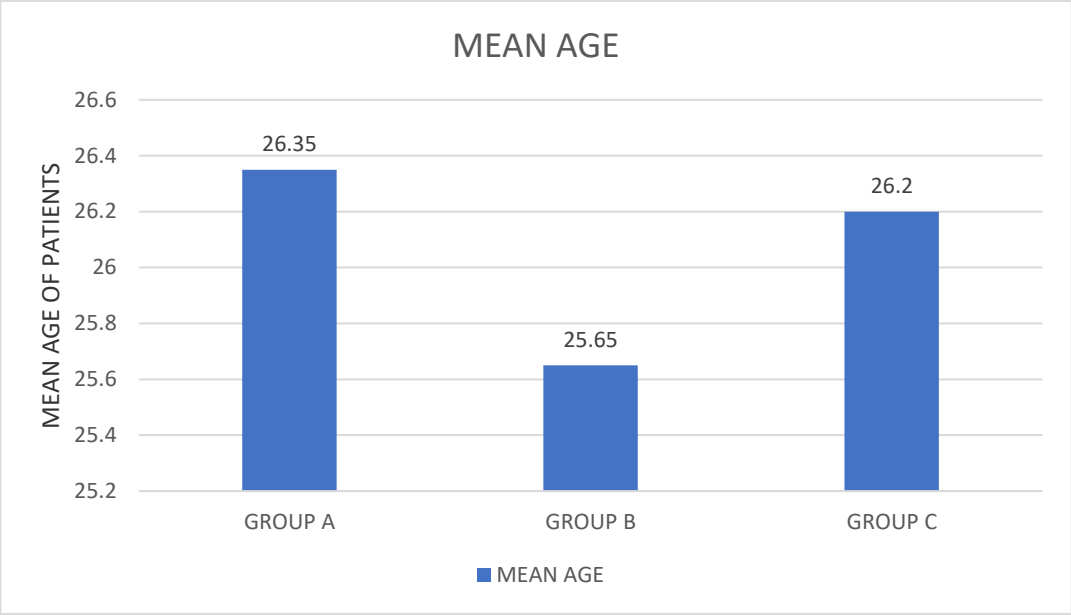


Figure 2 is the graphical representation of Table 2.

TABLE 3 – MARITAL STATUS

GROUP	MARRIED		UNMARRIED		TOTAL
	NO OF PATIENTS	%	NO OF PATIENTS	%	NO OF PATIENTS
GROUP A	12	60	8	40	20
GROUP B	11	55	9	45	20
GROUP C	12	60	8	40	20

Table 2 shows the marital status in all three groups.

Both group A and group C had maximum number of married women. Unmarried women were found maximum in group B.

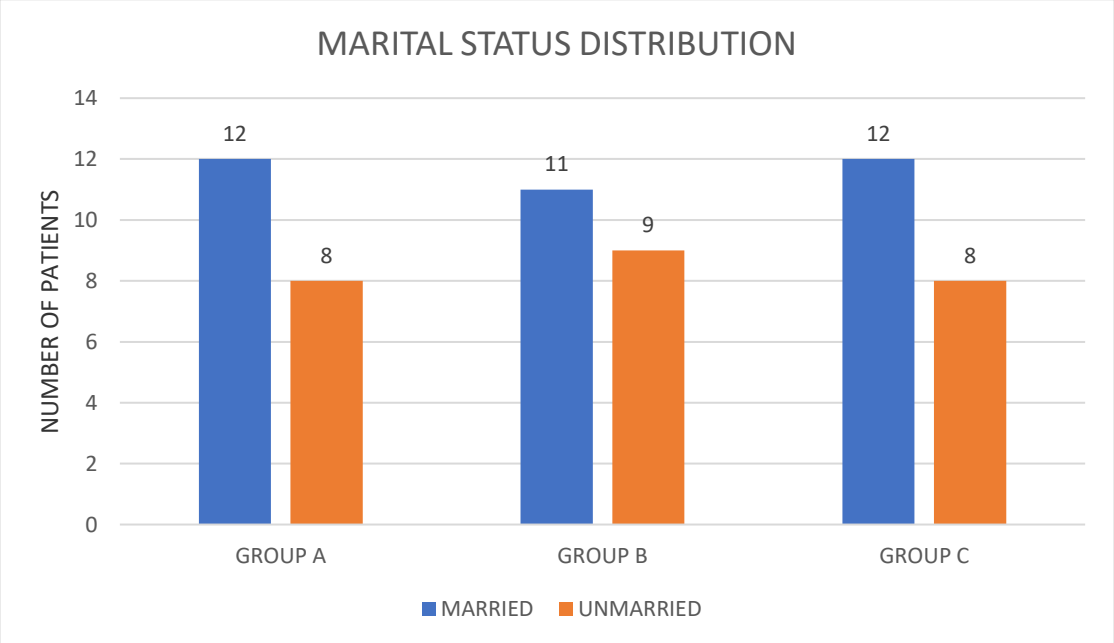


Figure 3 is the graphical representation of Table 3

TABLE 4 – BODY MASS INDEX (kg/m^2)

GROUP	0 – WEEKS		12 - WEEKS		P -VALUE
	MEAN	SD	MEAN	SD	
GROUP A	27.84	2.33	26.63	3.51	0.032
GROUP B	28.31	2.65	27.31	3.50	0.049
GROUP C	28.81	2.73	24.62	3.25	< 0.001
P – VALUE	0.499		0.042		

Table 4 shows mean body mass index in all three groups.

Statistical analysis within the groups showed significant difference in the body mass index at the end of 12 weeks.

Statistical analysis between the groups showed significant difference in the body mass index at the end of 12 weeks. (p=0.04)

FIGURE 4 – BODY MASS INDEX

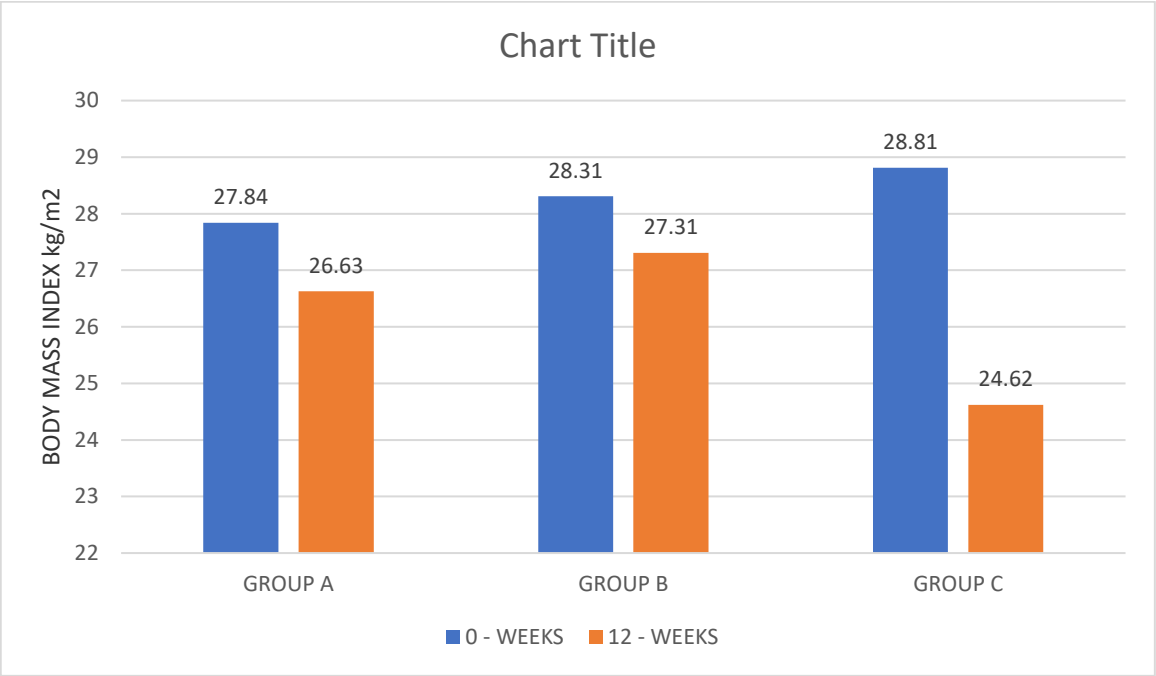


Figure 4 is the graphical representation of Table 4

TABLE 5 – SYSTOLIC BLOOD PRESSURE (mm/Hg)

GROUP	0 – WEEKS		12 – WEEKS		P – VALUE
	MEAN	SD	MEAN	SD	
GROUP A	114.80	12.57	114.00	13.10	0.163
GROUP B	112.90	13.41	112.20	13.05	0.149
GROUP C	115.60	12.44	114.90	12.28	0.149
P – VALUE	0.792		0.795		

Table 5 shows mean systolic blood pressure in all three groups.

Statistical analysis within the groups and between the groups did not show any significant difference in the systolic blood pressure at the end of 12 weeks

FIGURE 5: SYSTOLIC BLOOD PRESSURE

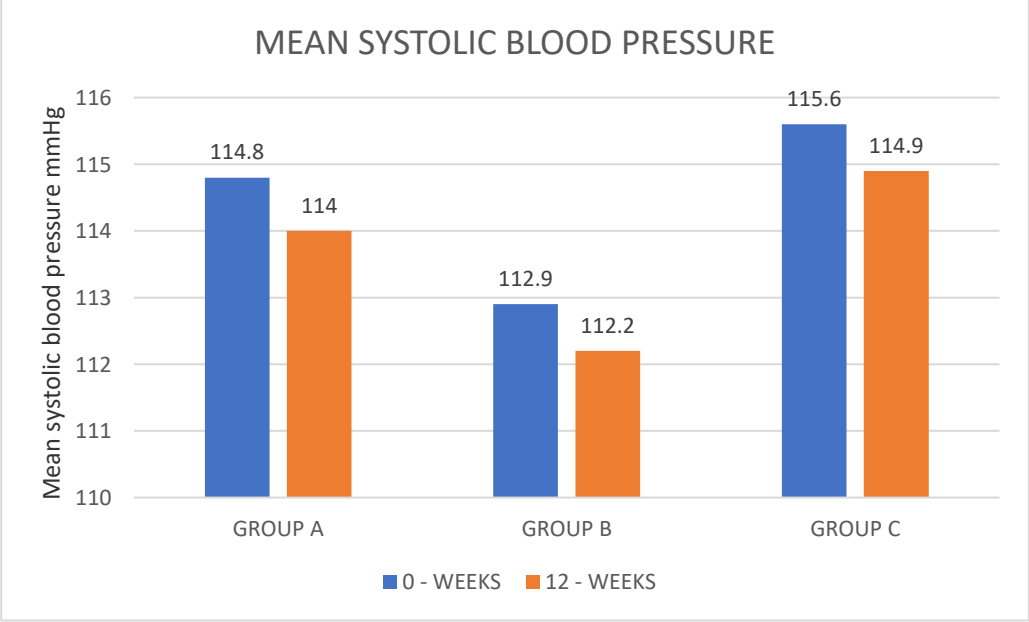


Figure 5 is the graphical representation of Table 5

TABLE 6 – DIASTOLIC BLOOD PRESSURE (mmHg)

GROUP	0 – WEEKS		12 – WEEKS		P – VALUE
	MEAN	SD	MEAN	SD	
GROUP A	71.70	5.88	71.20	6.06	0.234
GROUP B	70.60	6.19	70.20	6.35	0.408
GROUP C	72.10	6.50	71.50	6.41	0.209
P - VALUE	0.732		0.791		

 Table 6 shows mean diastolic blood pressure in all three groups.

No statistically significant difference was observed within the groups and between the groups in the diastolic blood pressure at the end of 12 weeks.

FIGURE 6: DIASTOLIC BLOOD PRESSURE

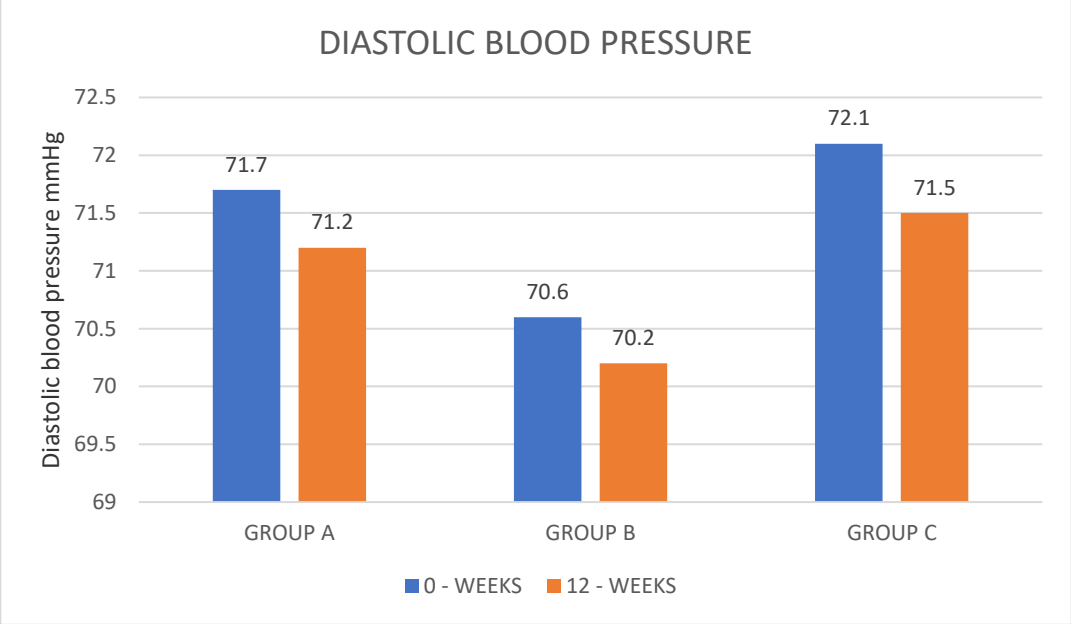


Figure 6 is the graphical representation of Table 6

TABLE 7 – MENSTRUAL CYCLE REGULARITY

GROUP	PATIENTS WITH REGULAR CYCLES 0 - WEEKS	%	PATIENTS WITH REGULAR CYCLES 12 – WEEKS	%
GROUP A	0	0	8	40
GROUP B	0	0	11	55
GROUP C	0	0	15	75

Table 7 shows number of patients who had regular menstrual cycles.

Menstrual cycle regularity was seen maximum in group C , followed by group B and group A.

FIGURE 7 – MENSTRUAL CYCLE REGULARITY

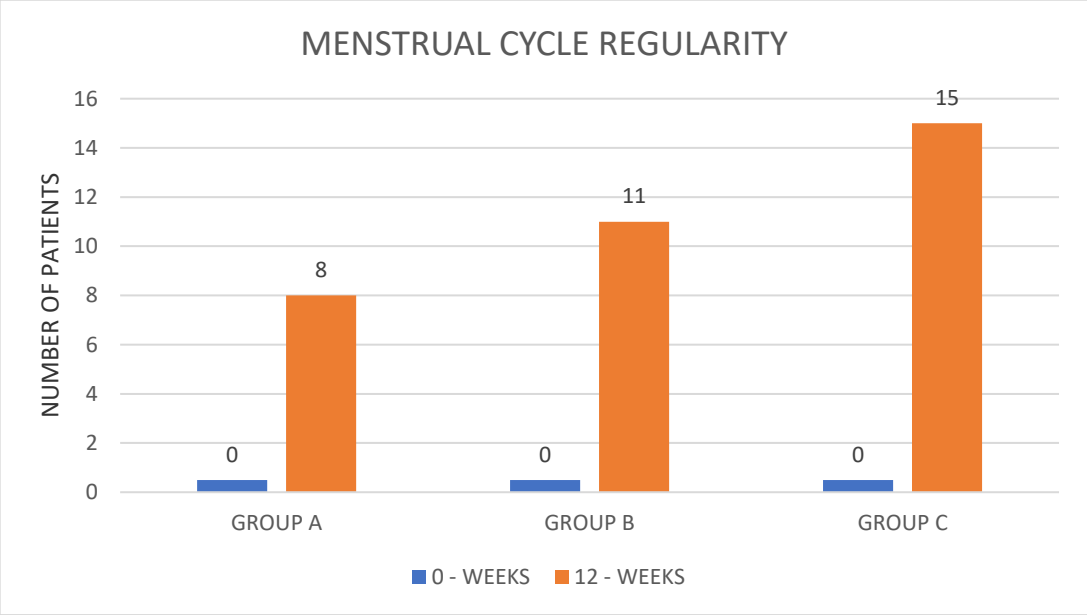


Figure 7 is the graphical representation of Table

TABLE 8 – FOLLICLE STIMULATING HORMONE (mIU/ml)

GROUP	0 – WEEKS		12 – WEEKS		P – VALUE
	MEAN	SD	MEAN	SD	
GROUP A	6.38	1.10	6.35	1.08	0.201
GROUP B	6.42	1.29	6.38	1.23	0.185
GROUP C	6.35	1.14	6.32	1.14	0.163
P - VALUE	0.985		0.987		

Table 8 shows mean FSH levels in all three groups at Baseline and at the end of 12 weeks.

There was no statistically no significant difference within the groups and between the groups at the end of 12 weeks.

FIGURE 8 – FOLLICLE STIMULATING HORMONE

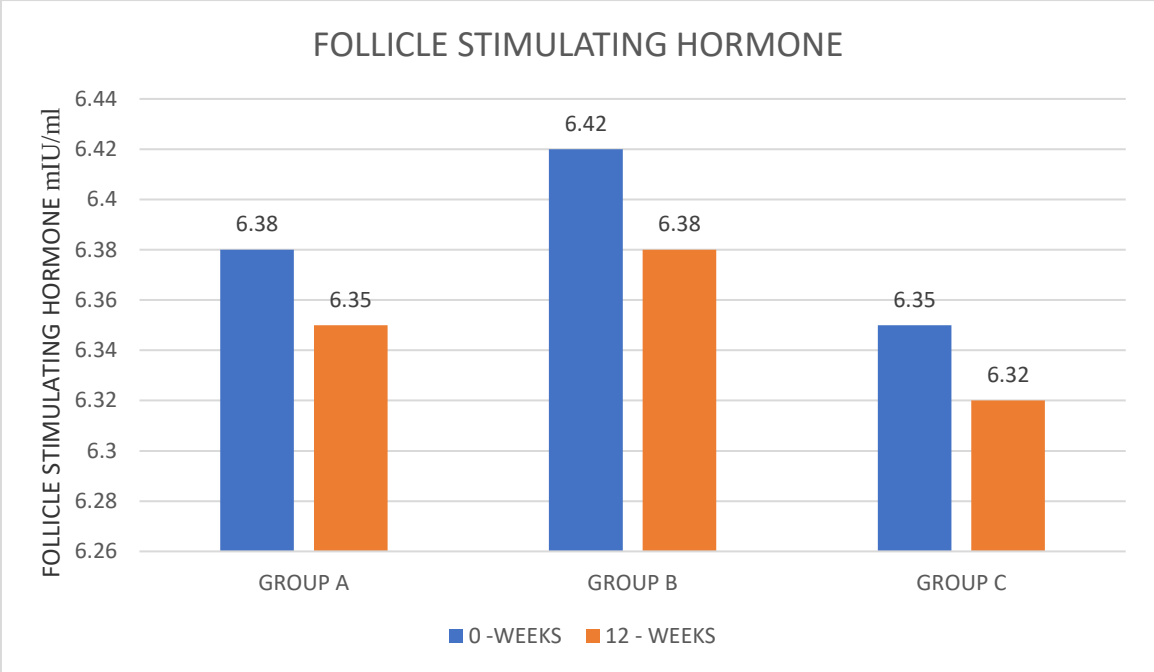


Figure 8 is the graphical representation of Table 8

TABLE 9 – LUTEINIZING HORMONE (mIU/ml)

GROUP	0 – WEEKS		12 – WEEKS		P – VALUE
	MEAN	SD	MEAN	SD	
GROUP A	14.79	2.14	14.47	2.04	0.023
GROUP B	15.60	3.28	13.82	3.03	0.001
GROUP C	16.26	2.96	11.88	3.11	< 0.001
P - VALUE	0.267		0.021		

Table 9 shows mean LH levels in all three groups at Baseline and at the end of 12 weeks.

 Statistical analysis within the groups showed a significant decrease in the LH level at the end of 12 weeks ($p<0.05$)

 Statistical analysis in between the groups showed a significant decrease in the LH level at the end of 12 weeks ($p=0.02$)

FIGURE 9 – LUTEINIZING HORMONE

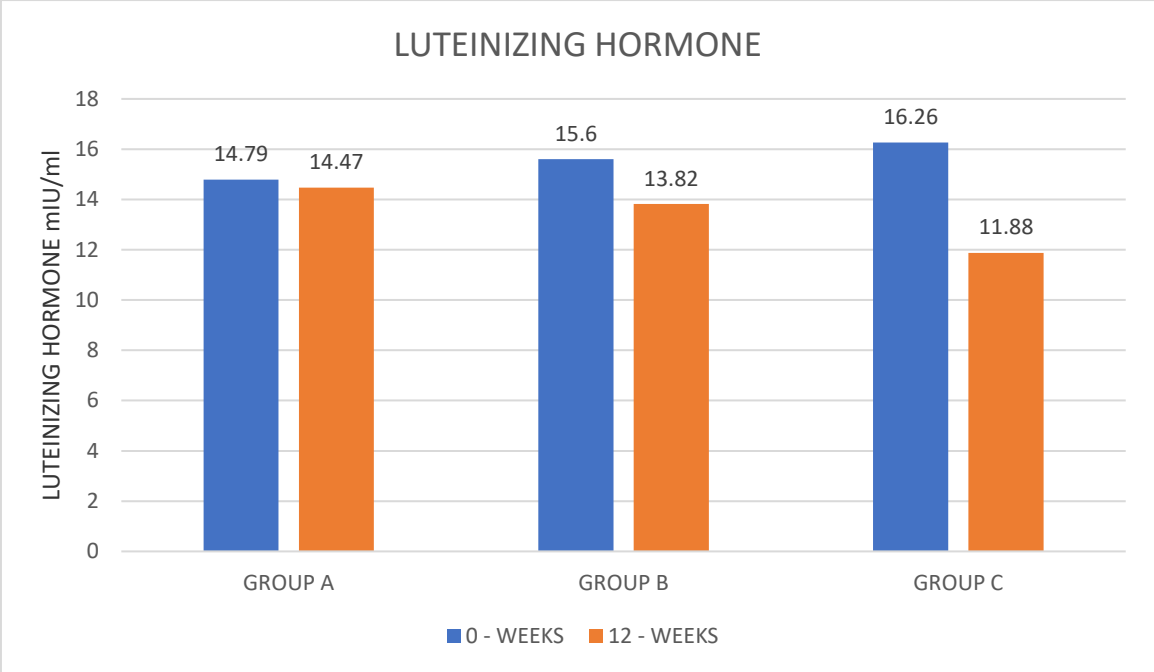


Figure 9 is the graphical representation of Table 9

TABLE 10 – FASTING BLOOD GLUCOSE (mg/dl)

GROUP	0 – WEEKS		12 – WEEKS		P – VALUE
	MEAN	SD	MEAN	SD	
GROUP A	112.20	10.38	107.60	7.22	<0.001
GROUP B	109.60	10.72	108.45	9.68	0.009
GROUP C	106.80	11.96	102.15	8.17	<0.001
P – VALUE	0.310		0.044		

Table 10 shows fasting blood glucose levels in all three groups at Baseline and at the end of 12 weeks.

 Statistical analysis within the groups showed a significant decrease in the fasting blood glucose levels at the end of 12 weeks ($p<0.05$)

 Statistical analysis in between the groups showed a significant decrease in the fasting blood glucose levels at the end of 12 weeks ($p=0.04$)

FIGURE 10 – FASTING BLOOD GLUCOSE (mg/dl)

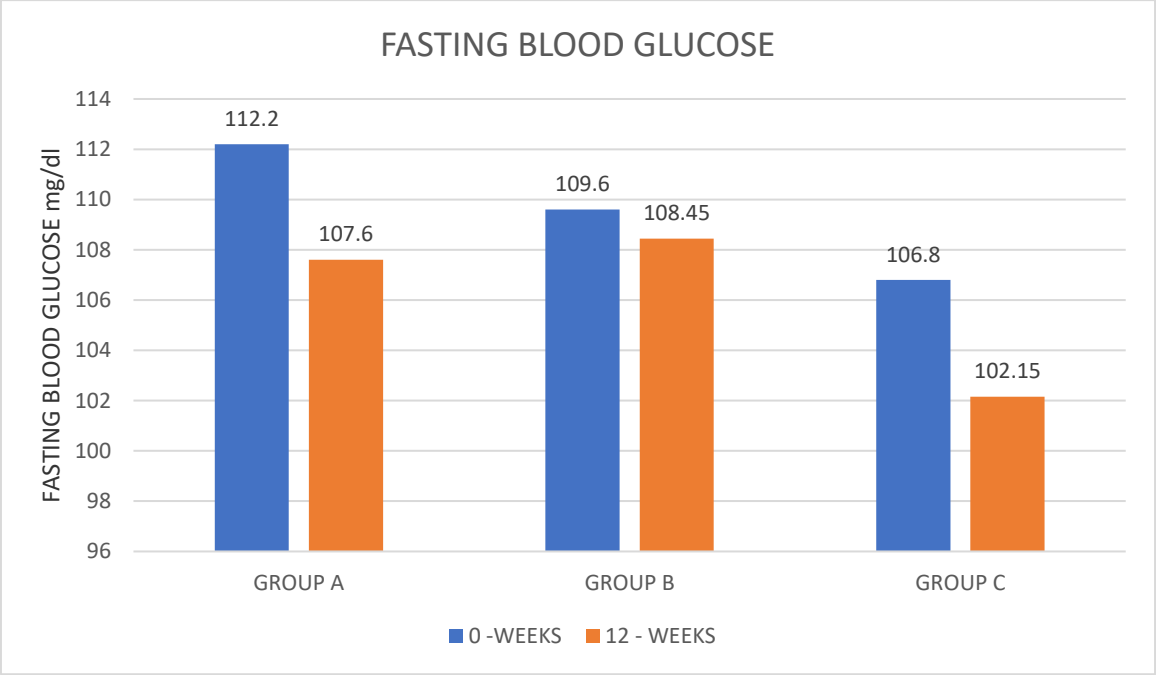


Figure 10 is the graphical representation of Table 10

TABLE 11 – FASTING SERUM INSULIN (µIU/ml)

GROUP	0 – WEEKS		12 – WEEKS		P – VALUE
	MEAN	SD	MEAN	SD	
GROUP A	14.40	5.94	11.79	3.64	0.001
GROUP B	15.90	6.03	14.05	4.71	0.001
GROUP C	17.16	6.52	10.07	2.90	< 0.0001
P - VALUE	0.372		0.007		

Table 11 shows fasting serum insulin levels in all three groups at Baseline and at the end of 12 weeks.

 Statistical analysis within the groups showed a significant decrease in the fasting serum insulin levels at the end of 12 weeks ($p<0.05$)

 Statistical analysis in between the groups showed a significant decrease in the fasting serum insulin levels at the end of 12 weeks ($p<0.05$)

FIGURE 11 – FASTING SERUM INSULIN

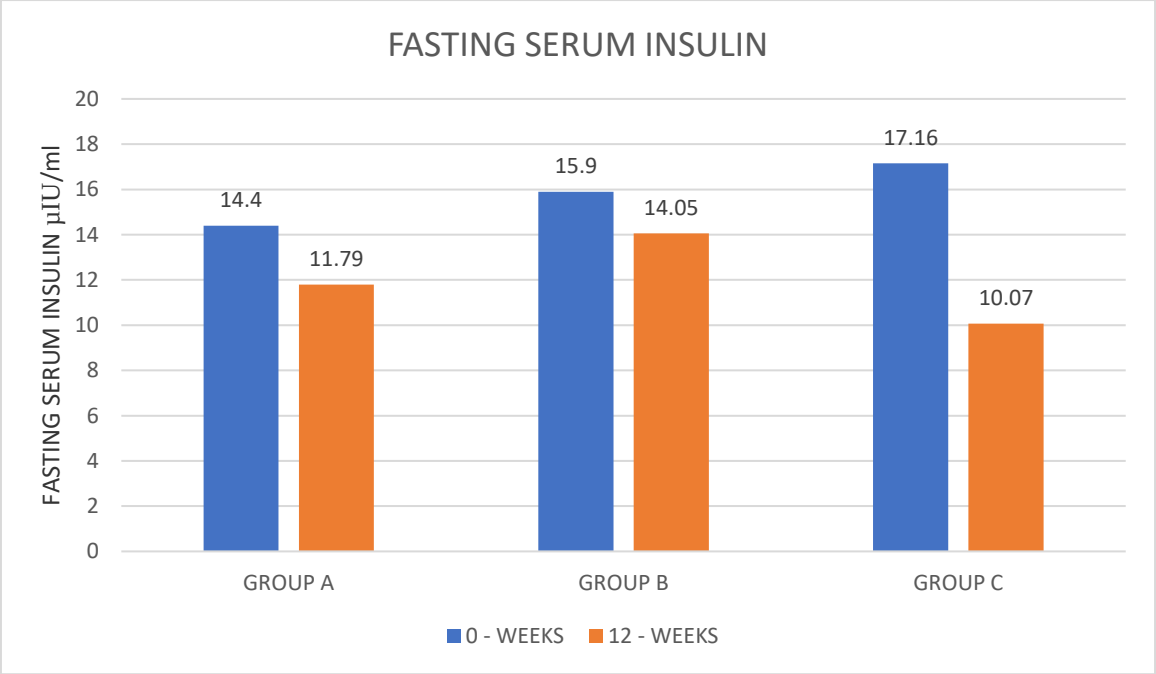


Figure 11 is the graphical representation of Table 11

TABLE 12 - NUMBER OF PREGNANCIES

GROUP	NO OF INFERTILE WOMEN AT 0 - WEEKS	NO OF PREGNANT WOMEN AT 20 - WEEKS	% OF PREGNANT WOMEN AT 20 WEEKS
GROUP A	9	3	33%
GROUP B	8	2	25%
GROUP C	10	4	40%

Table 12 shows number of patients with infertility at 0 weeks and number of patients who became pregnant at the end of 20 weeks.

FIGURE 12 - NUMBER OF PREGNANCIES

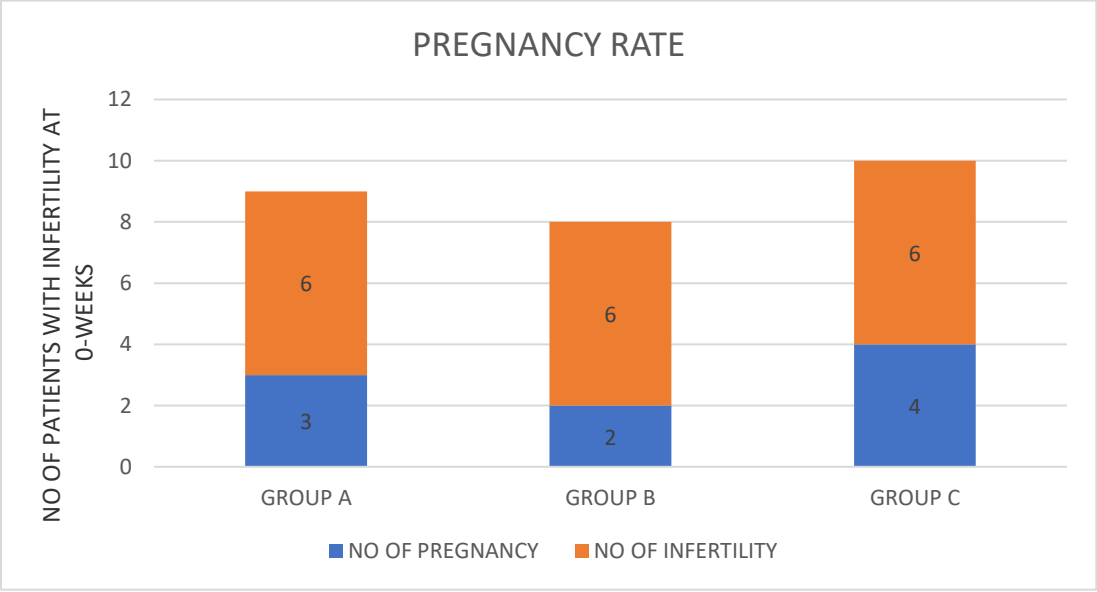


Figure 12 is the graphical representation of Table 12

TABLE 13: BIOCHEMICAL INVESTIGATIONS (FOR GROUP A)

INVESTIGATIONS	0 – WEEKS		12 – WEEKS		P – VALUE
	MEAN	SD	MEAN	SD	
HEMOGLOBIN	12.50	0.68	12.65	0.78	0.115
TOTAL COUNT	7885.00	1167.21	7610.00	1022.84	0.381
BL.UREA	25.87	6.19	25.65	6.11	0.404
SR.CREATININE	0.75	0.12	0.74	0.14	0.419
SGOT	26.45	4.28	26.15	3.97	0.445
SGPT	25.75	6.38	25.15	6.11	0.225

Table 13 shows the Biochemical and Hematological parameters of the group A. Statistical analysis within the groups and between the groups did not show any significant difference at 12 weeks.

TABLE 14 – BIOCHEMICAL INVESTIGATIONS (GROUP B)

INVESTIGATIONS	0 – WEEKS		12 – WEEKS		P – VALUE
	MEAN	SD	MEAN	SD	
HEMOGLOBIN	11.90	0.76	11.93	0.69	0.708
TOTAL COUNT	7835.00	1139.84	7780.00	1154.21	0.881
BL.UREA	25.05	6.35	24.92	6.34	0.134
SR.CREATININE	0.76	0.12	0.75	0.16	0.666
SGOT	27.00	4.70	26.20	5.38	0.414
SGPT	24.85	5.27	24.70	5.02	0.757

Table 14 shows the Biochemical and Hematological parameters of the group B.

Statistical analysis within the groups and between the groups did not show any significant difference at 12 weeks.

TABLE 15 - BIOCHEMICAL INVESTIGATIONS (GROUP C)

INVESTIGATIONS	0 – WEEKS		12 – WEEKS		P – VALUE
	MEAN	SD	MEAN	SD	
HEMOGLOBIN	11.83	0.61	11.71	0.57	0.344
TOTAL COUNT	8055.00	1060.02	7855.00	1011.23	0.583
BL.UREA	27.25	6.07	27.11	6.03	0.848
SR.CREATININE	0.75	0.12	0.74	0.15	0.772
SGOT	26.95	6.13	26.60	5.69	0.427
SGPT	27.45	5.06	26.92	4.91	0.275

Table 15 shows the Biochemical and Hematological parameters of the group C.

Statistical analysis within the groups and between the groups did not show any significant difference at 12 weeks.

TABLE 16: INCIDENCE OF ADR

	GROUP A	GROUP B	GROUP C
NUMBER OF ADRs	6	3	6

Table 16 shows the incidence of ADRs presented by the patients in all three groups.

In group A, 6 ADRs were reported, in group B - 3 ADRs were reported and in group C - 6 ADRs were reported.

FIGURE 13: INCIDENCE OF ADR

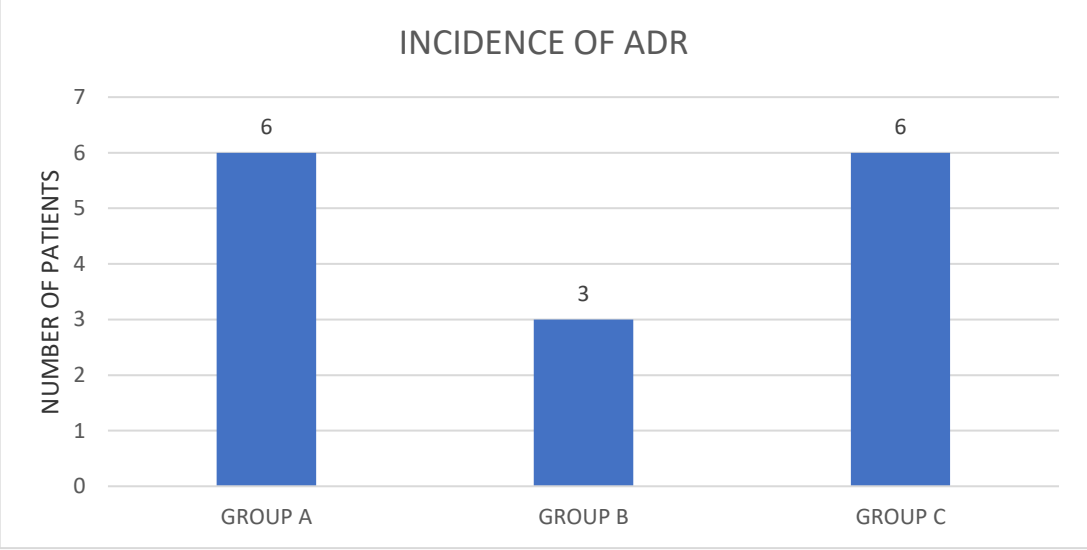


Figure 13 shows the graphical representation of incidence of ADRs.

TABLE 17 - ADVERSE DRUG REACTIONS

ADR	GROUP A	GROUP B	GROUP C
Nausea	2 (10%)	1 (5%)	2 (10%)
Abdomen pain	2 (10%)	2 (10%)	2 (10%)
Diarrhoea	2 (10%)	-	1 (5%)
Headache	-	-	1 (5%)

Table 17 shows the adverse effect profile of all three groups.

Gastrointestinal disturbances were more commonly reported in all the groups.

FIGURE 14: INCIDENCE OF ADR

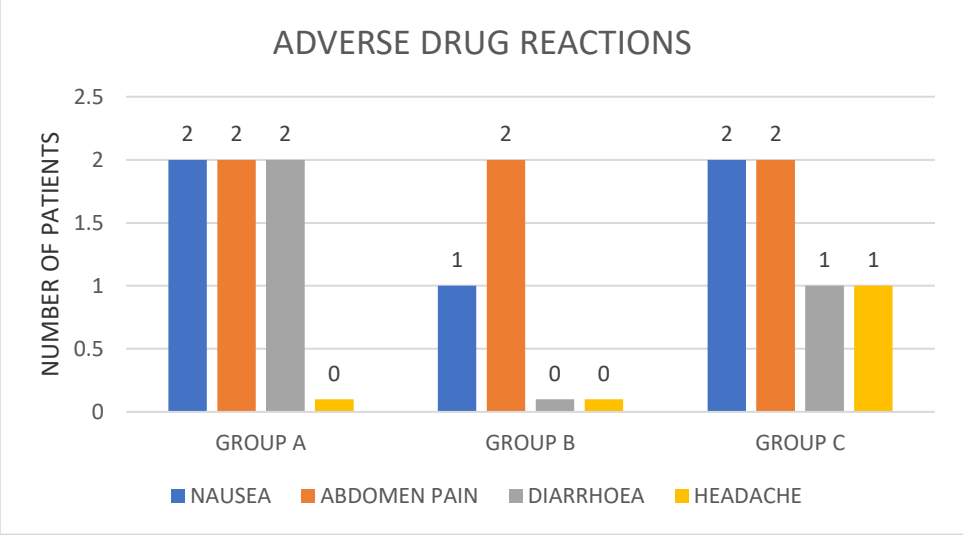


Figure 14 is the graphical representation of adverse drug reactions in 3 groups.

TABLE 18 - SEVERITY ASSESSMENT OF ADR

SEVERITY	GROUP A	GROUP B	GROUP C
MILD	6	3	6
MODERATE	-	-	-
SEVERE	-	-	-

Table 18 shows severity assessment of Adverse Drug Reactions.

- Severity assessment was done using Modified Hartwig and Siegel scale.
- All the Adverse Drug Reactions in three groups were mild.

TABLE 19 : CAUSALITY ASSESSMENT OF INDIVIDUAL ADR IN GROUP A

ADR	Certain	Probable	Possible	Unlikely	Unclassified	Unclassifiable	Total
Nausea			2				2
Abdomen pain			2				2
Diarrhoea			2				2
Headache			-				-
Total			6				6

Table 19 shows causality assessment of individual ADR in group A.

- Causality assessment was done using WHO causality assessment scale
- All adverse drug reactions were categorized as possible.

TABLE 20 : CAUSALITY ASSESSMENT OF INDIVIDUAL ADR IN GROUP B

ADR	Certain	Probable	Possible	Unlikely	Unclassified	Unclassifiable	Total
Nausea			1				1
Abdomen pain			2				2
Diarrhoea			-				-
Headache			-				-
Total			3				3

Table 20 shows causality assessment of individual ADR in group B.

All ADRs were categorized as possible under WHO causality assessment scale.

TABLE 21 : CAUSALITY ASSESSMENT OF INDIVIDUAL ADR IN GROUP C

ADR	Certain	Probable	Possible	Unlikely	Unclassified	Unclassifiable	Total
Nausea			2				2
Abdomen pain			2				2
Diarrhoea			1				1
Headache			1				1
Total			6				6

Table 21 shows causality assessment of individual ADR in group C.

All ADRs were categorized as possible under WHO causality assessment scale.

DISCUSSION

DISCUSSION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder of women of reproductive age group. It is the most common cause of infertility due to menstrual dysfunction. [1] PCOS is a complex heterogenous disorder with features of oligomenorrhoea, anovulation, and signs of androgen excess like hirsutism, acne, male type baldness and multiple cysts in both ovaries.

PCOS is of multifactorial etiology and attributed to familial, genetic and environmental factors. Multiple gene mutations are associated with pathogenesis. Positive family history among siblings and offspring is also noted. About 60 – 70% of cases are associated with **insulin resistance (IR).** It is due to abnormality in insulin receptor mediated signal transduction. Some actions of insulin are mediated by inositol phosphoglycan mediators. Deficient release of a putative D-chiro-inositol containing inositol phosphoglycan (DCI-IPG) mediator may contribute to insulin resistance in women with polycystic ovary syndrome (PCOS).

IR leads to compensatory hyperinsulinemia. This excess insulin stimulates luteinizing hormone (LH) to produce more androgens from ovary leading to hyperandrogenism. Also, inappropriate gonadotropin secretion leads to preferential production of luteinizing hormone (LH) compared to follicle stimulating hormone (FSH) [1,7] and LH:FSH ratio becomes 2:1 or even 3:1[4] . This vicious cycle leads to increased insulin, LH and androgen levels. These lead to anovulation, menstrual irregularity and infertility.

Complications of PCOS include infertility, risk of endometrial and breast cancers in later life. Metabolic complications include type 2 diabetes mellitus, obesity, dyslipidemia, atherosclerosis and coronary artery disease.

Life style modifications like regular exercise and balanced diet are the main stay of treatment. Unmarried, adolescent girls with hyperandrogenism need anti androgens and hormonal contraceptives for cycle regularization. Married women with infertility need ovulation induction. In addition, insulin sensitizers like metformin are used to avoid and treat metabolic disorders associated with IR.

Inositol is a physiological compound of sugar family of which two stereoisomers are found in our body, myoinositol (MI) and D-chiro inositol (DCI). DCI is synthesized endogenously from MI by insulin dependent epimerase enzyme. DCI is an important second messenger in insulin signal transduction. It acts as a precursor for inositol triphosphate (IP3) and phosphatidyl inositol 3 kinase (PI3K), needed for actions of insulin like increased glucose uptake, thus improving insulin sensitivity. Thus, DCI can be used as an alternative to metformin to improve insulin sensitivity.

The patients for the study were screened by history, clinical examination and laboratory investigations. Among 108 patients, 58 patients who did not meet the inclusion criteria were excluded. 60 patients who fulfilled the eligibility criteria were enrolled and randomized into three groups, 20 patients in each group. Group A received Tab Metformin 500mg TDS and the Group B received Tab D-chiro inositol 600mg OD (wt < 60kg) or 600mg BD (wt> 60kg) and Group C received Tab Metformin plus

Tab D-chiro inositol for 12 weeks duration and all three groups were followed up for 8 weeks. There were no drop outs in the study.

Body mass index, systolic and diastolic blood pressure, serum FSH and LH levels, fasting glucose and insulin levels and regularity of menstrual cycle were assessed. The results were analyzed statistically using **Paired t-test and ANOVA (analysis of variance).**

Among the 60 patients who completed the study, the **mean age** was 26.3 years in group A, 25.6 years in group B and 26.2 years in group C. The mean age distribution was comparable in all three groups and there was no significant difference between the groups. Also, marital status did not show any statistically significant difference between the groups. This shows that all the patients belonged to the same population.

The systolic and diastolic blood pressure did not show any significant difference between the groups at the end of 12 weeks. This shows that the addition of D-chiro inositol did not affect these parameters.

At 0 weeks, the **mean body mass index** was 27.84 kg/m2 in group A, 28.31 kg/m2 in group B and 28.81 kg/m2 in group C. At the end of 12 weeks, the mean BMI was reduced to 26.63 kg/m2 in group A ($p=0.03$), 27.31 kg/m2 in group B ($p=0.04$) and 24.62 kg/m2 in group C ($p<0.001$). Intergroup analysis using ANOVA showed that all three groups were comparable at baseline ($p=0.49$) but there was significant reduction in BMI between the three groups at the end of 12 weeks ($p=0.04$).

This shows that combining metformin with DCI helps in greater weight reduction than when given alone.

The mean FSH levels did not show any significant difference between the groups at the end of 12 weeks. This shows D-chiro inositol has no effect on FSH.

At 0 weeks, the **mean LH levels** were 14.79 mIU/ml in group A, 15.60 mIU/ml in group B and 16.26 mIU/ml in group C. At the end of 12 weeks, the mean LH levels reduced to 14.47 mIU/ml in group A ($p=0.02$), 13.82 mIU/ml in group B ($p=0.001$) and 11.88 mIU/ml in group C ($p<0.001$). Intergroup analysis using ANOVA showed that all three groups were comparable at baseline ($p=0.26$) and there was significant reduction in LH levels between the three groups at the end of 12 weeks ($p=0.02$). This shows that combining metformin with DCI helps in greater reduction of LH levels.

At 0 weeks, the **mean fasting blood glucose levels** were 112.20 mg/dl in group A, 109.60 mg/dl in group B and 106.80 mg/dl in group C. At the end of 12 weeks, the mean fasting blood glucose levels reduced to 107.60 mg/dl in group A ($p<0.001$), 108.45 mg/dl in group B ($p=0.009$) and 102.15 mg/dl in group C ($p<0.001$). Intergroup analysis using ANOVA showed that all three groups were comparable at baseline ($p=0.31$) and there was significant reduction in mean fasting blood glucose levels between the three groups at the end of 12 weeks ($p=0.04$). This shows that combining metformin with DCI helps in greater reduction of mean fasting blood glucose levels.

At 0 weeks, the **mean fasting serum insulin levels** were 14.40 µIU/ml in group A, 15.90 µIU/ml in group B and 17.16 µIU/ml in group C. At the end of 12 weeks, the mean fasting serum insulin levels reduced to 11.79 µIU/ml in group A ($p=0.001$), 14.05 µIU/ml in group B ($p=0.001$) and 10.07 µIU/ml in group C ($p<0.001$). Intergroup analysis using ANOVA showed that all three groups were comparable at baseline ($p=0.37$) and there was significant reduction in mean fasting serum insulin levels between the three groups at the end of 12 weeks ($p=0.007$). This shows that combining metformin with DCI helps in greater reduction of mean fasting serum insulin levels.

At 0 weeks, all 60 patients in three groups had irregular menstrual cycle. At the end of 12 weeks, 40% of patients in group A, 55% of patients in group B and 75% of patients in group C resumed **regular menstrual cycles**. Statistical significance was seen in between the groups using ANOVA at the end of 12 weeks treatment.

At 0 weeks, 9 women of group A, 8 women of group B and 10 women of group C were infertile. During follow up period (4^{th} and 5^{th} month of study), we noted that 3 women in group A, 2 women of group B and 4 women of group C **became pregnant.**

Our study results were also similar to the study conducted by Nestler et al, where supplementation of 1200mg of D-chiro inositol for a period of 8 weeks reduced serum insulin and blood glucose levels in women with PCOS and restored ovulation in about 86% of patients.

In Lagana et al study, a 6 month of supplementation of 1 gram of DCI showed significant reduction in serum LH level, serum insulin and blood glucose levels and resumption of regular menstrual cycles.

In Genazzani et al study, DCI 500mg OD for 12 weeks showed a significant reduction in BMI, serum LH level, serum insulin levels.

Antonio et al, conducted a retrospective study in 47 patients treated with DCI showed that percentage of women reporting regular menstrual cycles significantly increased with increasing duration of DCI treatment and no significant adverse effects were noted in patients treated with DCI even upto 15 months. This is to indicate safety profile of DCI even in long term administration.

The **hematological parameters** like hemoglobin, total count did not show any significant difference in all three groups at the end of 12 weeks. There was no significant difference in biochemical parameters like blood urea, serum creatinine, SGOT, SGPT in all three groups at the end of the study period. This shows that addition of D-chiro inositol did not alter the hematological and biochemical parameters.

Mild adverse effects like nausea, abdominal pain, and diarrhea was observed in all three groups. Headache probably due to hypoglycemia was noted in 1 patient in group C. Totally 30% of group A patients (n=6), 15% of group B patients (n=3) and 30% of group C patients (n=6) developed these adverse effects.

There was a significant reduction in body mass index, serum LH level, fasting blood glucose and serum insulin levels and regulation of menstrual cycles was seen at the end of 12 weeks in all three groups but more significant in group C receiving metformin with DCI. All these effects were sustained even after withdrawal, during 8 weeks follow up period.

It is thus evident that DCI administration helps to improve insulin sensitivity and can be used in women with PCOS having insulin resistance. DCI helps in reducing metabolic and endocrinological abnormalities in PCOS patients. Effects are more pronounced when DCI is given along with metformin.

The number of adverse events observed were less in patients receiving D - chiroinositol compared to patients receiving metformin. According to WHO causality assessment scale, all the Adverse Drug Reactions observed were categorized as possible. Based on the Modified Hartwig and Siegel severity assessment scale, all the reactions reported were mild. This explicits that D-chiroinositol did not increase the occurrence of adverse events.

As evidenced by earlier studies, our study has also observed that DCI has caused significant reduction in body mass index, serum LH level, fasting blood glucose and serum insulin levels and regulation of menstrual cycles. Addition of DCI has not produced any significant changes in the hematological and biochemical parameters. Also the observed adverse drug effects were mild and resulted in significant improvement in the patients' quality of life.

The **limitations of our study** are that it was done for a shorter period and also in small group of patients. Effect of DCI in various hormone levels like androgen levels and other metabolic parameters like lipid levels were not monitored. Further studies are needed to be done in larger group of patients for longer duration to prove its effect in polycystic ovary syndrome.

CONCLUSION

CONCLUSION

From our study, we conclude that in patients with polycystic ovary syndrome who are obese and have insulin resistance with hyperinsulinemia,

- D-chiroinositol as add on therapy to metformin is effective in reducing LH levels, blood glucose and serum insulin levels.
- DCI aids in weight reduction, regularization of menstrual cycles and ovulation and increases chances of pregnancy.
- D-chiroinositol is well tolerated. No significant adverse effects were noted.

Thus, DCI can be a treatment option along with metformin for patients with polycystic ovary syndrome with insulin resistance.

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APPENDICES

APPENDIX - I

LIST OF ABBREVIATIONS USED

PCOS	-	Polycystic ovary syndrome
IR	-	Insulin resistance
FSH	-	Follicle stimulating hormone
LH	-	Luteinizing hormone
ESHRE/ ASRM	-	European society for human reproduction and embryology American society for reproductive medicine
DCI	-	D chiro inositol
MI	-	Myo inositol
GnRH	-	Gonadotropin releasing hormone
USG	-	Ultrasonogram
FBS	-	Fasting blood sugar
PPBS	-	Postprandial blood sugar
SHBG	-	Sex hormone binding globulin
DHEA - S	-	Dehydroepiandrosterone sulphate
SGOT	-	Serum glutamate oxaloacetate transaminase
SGPT	-	Serum glutamate pyruvate transaminase
IRS	-	Insulin receptor substrate
BMI	-	Body mass index
HOMA – IR	-	Homeostasis model assessment – Insulin resistance

APPENDIX – II

CASE REPORT FORM

A Prospective, Randomized, Open label, Comparative study of D-chiro inositol with metformin in patients with polycystic ovary syndrome"

PATIENT DEMOGRAPHY:

NAME : ADDRESS :

AGE/SEX : CONTACT NO :

OP No :

DIAGNOSIS :

MEDICAL HISTORY:

VISIT 1

CHIEF COMPLAINTS:

PAST HISTORY:

PERSONAL HISTORY:

MENSTRUAL HISTORY:

GENERAL EXAMINATION:

Pulse rate: BP: Ht: Wt: BMI:

LAB INVESTIGATIONS:

COMPLETE BLOOD COUNT: Hemoglobin:	TC: DC:
ESR	
Fasting blood glucose	
Postprandial blood glucose	
Serum cholesterol	
LIVER FUNCTION TEST: Serum bilirubin SGOT SGPT	
RENAL FUNCTION TEST: Blood urea Serum creatinine	
THYROID FUNCTION TEST: TSH Free T3 Free T4	

Serum FSH	
Serum LH	
Fasting serum insulin	
Urine analysis	
Pelvic ultrasonogram	

TREATMENT:

VISIT 2 (4th week)

H/O menstrual cycle regularity

CLINICAL EXAMINATION:

Pulse rate: BP: Ht: Wt: BMI:

Adverse events:

VISIT 3 (8th week)

H/O menstrual cycle regularity

CLINICAL EXAMINATION:

Pulse rate: BP: Ht: Wt: BMI:

Adverse events:

VISIT 4 (12th week)

H/O menstrual cycle regularity

CLINICAL EXAMINATION:

Pulse rate: BP: Ht: Wt: BMI:

Adverse events:

FOLLOW UP

VISIT 5 (16th week)

H/O menstrual cycle regularity

Ht: Wt: BMI:

VISIT 6 (20th week)

H/O menstrual cycle regularity

Ht: Wt: BMI:

PARAMETERS	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6
Menstrual cycle regularity						
Body mass index (BMI)						
Serum FSH						
Serum LH						

Fasting blood glucose						
Fasting serum insulin						
Adverse events						

Name of the doctor:

Signature:

Date:

APPENDIX – III

INFORMED CONSENT FORM

Title: "A Prospective, Randomized, Open label, Comparative study of D-chiro inositol with metformin in patients with polycystic ovary syndrome"

Name of the Participant:

I …….. have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in this study.

1. I have read and understood this consent form and the information provided to me.

2. I have had the consent document explained to me.

3. I have been explained about the nature of the study.

4. I have been explained about my rights and responsibilities by the investigator.

5. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital.

6. I hereby give permission to the investigators to release the information obtained from me as a result of participation in this study to the sponsors, regulatory authorities, Govt. agencies and IEC.

7. I understand that my identity will be kept confidential if my data are publicly presented.

8. I have had my questions answered to my satisfaction.

9. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document.

1. Name and signature / thumb impression of the participant (or legal representative if participant incompetent)

Name ……. Signature …….. Date

2. Name and signature of impartial witness (required for illiterate patients)

Name ……. Signature ……..... Date

Address and contact number of the impartial witness:

3. Name and signature of the investigator or his representative obtaining consent:

Name …… Signature …… Date

சுய ஒப்புதல் படிவம்

ஆய்வு தலைப்பு

பாலி சிஸ்டிக் ஒவேரியன் சிண்ட்ரோம் எனும் நோயின் சிகிச்சையில் டி-கைரோ ஐயனோசிடால் என்னும் மருந்தின் பங்கு பற்றியும் அதன் விளைவுகள் பற்றியும் ஒரு திறந்தநிலை ஒப்பீட்டு ஆய்வு.

ஆய்வாளர்:

பங்கேற்பாளர்:

பெயர்: வயது: தேதி: உள்நோயாளி எண்

_____ என்பவராகிய நான் இந்த ஆய்வின் விவரங்களும் அதன் நோக்கங்களும் பற்றி முழுமையாக அறிந்து கொண்டேன். எனது சந்தேகங்கள் அனைத்திற்கும் தகுந்த விளக்கம் அளிக்கப்பட்டது. இந்த ஆய்வில் முழு சுதந்திரத்துடன் மற்றும் சுயநினைவுடன் பங்கு கொள்ள சம்மதிக்கிறேன்.

எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்து கொண்டு நான் எனது சம்மதத்தைத் தெரிவிக்கிறேன். இச்சுய ஒப்புதல் படிவத்தை பற்றி எனக்கு விளக்கப்பட்டது.

இந்த ஆய்வினை பற்றிய அனைத்து தகவல்களும் எனக்கு தெரிவிக்கப்படடது. இந்த ஆய்வில் எனது உரிமை மற்றும் பங்கினை பற்றிய அறிந்து கொண்டேன்.

இந்த ஆய்வில் பிறரின் நிர்பந்தமின்றி என் சொந்த விருப்பத்தின் பேரில் நான் பங்கு பெறுகிறேன் மற்றும் நான் இந்த ஆராய்ச்சியிலிருந்து எந்நேரமும் பின் வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்து கொண்டேன்.

இந்த ஆயவில் கலந்து கொள்வதன் மூலம் என்னிடம் பெறப்படும் தகவலை ஆய்வாளர் இன்ஸ்ட்டியூசனல் எத்திக்ஸ் கமிட்டியினரிடமோ, அரசு நிறுவனத்திடமோ தேவைப்பட்டால் பகிர்ந்து கொள்ளலாம் என சம்மதிக்கிறேன்.

இந்த ஆய்வின் முடிவுகளை வெளியிடும்போது எனது பெயரோ, அடையாளமோ வெளியிடப்படாது என அறிந்து கொண்டேன். இந்த ஆய்வின் விவரங்களைக் கொண்ட தகவல் தாளைப் பெற்றுக் கொண்டேன். இந்த ஆய்விற்காக இரத்தப் பாசோதனை செய்துக் கொள்ள சம்மதிக்கிறேன்.

இந்த ஆய்வில் பங்கேற்கும் பொழுது ஏதேனும் சந்தேகம் ஏற்பட்டால், உடனே ஆய்வாளரை தொடர்பு கொள்ள வேண்டும் என அறிந்து கொண்டேன்.

இந்சுய ஒப்புதல் படிவத்தில் கையெழுத்திடுவதன் மூலம் இதிலுள்ள அனைத்து விஷயங்களும் எனக்கு தெளிவாக விளக்கப்பட்டது என்றும் தெரிவிக்கிறேன். இச்சுய ஒப்புதல் படிவத்தின் நகல் ஒன்று எனக்குக் கொடுக்கப்படும் என்றும் தெரிந்து கொண்டேன்.

பங்கேற்பாளர் / பாதுகாவலர் கையொப்பம் தேதி:

ஆய்வாளர் கையொப்பம் தேதி:

APPENDIX - IV

INFORMATION TO PARTICIPANTS

"A PROSPECTIVE, RANDOMIZED, OPEN LABEL, COMPARATIVE STUDY OF D-CHIROINOSITOL WITH METFORMIN IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME"

Principal investigator:

Name of the participants:

This study is conducted in Rajiv Gandhi Government General hospital / Institute of Obstetrics and Gynaecology, Chennai. You are invited to take part in the study. The information in this document is meant to help you decide whether to take part or not. Please feel free to ask if you have any queries or concerns.

Purpose of the study:

Polycystic ovary syndrome is the most common cause of infertility in women due to menstrual dysfunction. It is associated with insulin resistance, leading to anovulation and increased androgen levels. D-chiro inositol helps to improve insulin sensitivity and thereby restoration of menstrual cycles and regulation of hormone levels. In this study, we compare the effects of D-chiro inositol with metformin. We have obtained permission from the Institutional Ethics Committee.

Study design:

All patients in the study will be divided into 3 groups A, B and C. You will be assigned to either of the groups. Group A will receive standard treatment (metformin), group B will receive D-chiroinositol and group C will receive both.

Study procedure:

Women with PCOS attending gynaecology OPD with irregular cycles, features of excess androgen like acne, hirsutism will be advised for blood glucose, serum insulin, FSH, LH levels and pelvic ultrasonogram. Those willing for the study will be divided inti 3 groups and treatment given for 12 weeks. The study involves evaluation of decrease in body weight, serum LH, blood glucose, serum insulin levels and regulation of menstrual cycles. The planned scheduled visits involve visits at 4^{th}, 8^{th}, 12^{th}, 16^{th}, 20^{th} week after your initial visit. At each visit, study physician will examine you. Blood tests

will be carried out twice during the study (at screening and at the end of 12th week) and about 6ml of blood will be collected. These tests are essential to monitor your condition and to assess the safety and efficacy of the treatment given to you.

In addition, if you notice any adverse events, you have to report it. You will be required to return unused study medicines when you report for your visits. This will enable correct assessment of the study results.

Possible benefits to you:

D-chiro inositol will cause reduction in body weight, serum LH, blood glucose, serum insulin levels and regulation of menstrual cycle.

Possible benefits to other people:

The results of the study may provide benefits to the society in terms of advancement of medical knowledge and/or therapeutic benefit for patients.

Confidentiality of the information obtained from you:

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examination, investigations, and your medical history). By signing this document, you will be allowing the research team investigators, other study personnel and Institutional Ethics Committee and any other person or agency by law like the Drug Controller General of India to view your data, if required. The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

Decision not to participate in the study:

Your decision not to participate in this study will not affect your medical care or your relationship with the investigator or the institution. You will be taken care of and you will not lose any benefits to which you are entitled.

Decision to withdraw from the study once you started:

The participation in this study is purely voluntary and you have the right to withdraw from this study at any time during the course of the study without giving any reasons. However, it is advisable that you talk to the research team prior to stopping the treatment/discontinuing the procedures etc. The results of this study will be informed to you at the end of the study.

Signature of Investigator | Signature of Participant

Date | Date

ஆய்வு தகவல் தாள்

ஆய்வு தலைப்பு

பாலி சிஸ்டிக் ஒவேரியன் சிண்ட்ரோம் எனும் நோயின் சிகிச்சையில் டி-கைரோ ஐயனோசிடால் என்னும் மருந்தின் பங்கு பற்றியும் அதன் விளைவுகள் பற்றியும் ஒரு திறந்தநிலை ஒப்பீட்டு ஆய்வு.

ஆய்வாளர்:

பங்கேற்பாளர்:

இந்த ஆய்வு இராஜீவ்காந்தி அரசு பொது மருத்துவமனை மற்றும் மகப்போறு மருத்துவமனை எழும்பூர், சென்னையில் நடைபெற உள்ளது.இந்த ஆய்வில் நீங்களும் பங்கேற்க விரும்புகிறோம். இதிலுள்ள தகவலின் அடிப்படையில் இந்த ஆய்வில் பங்கேற்பதா அல்லது வேண்டாமா என்று நீங்கள் முடிவு செய்து கொள்ளலாம். உங்கள் சந்தேகங்களை எங்களிடம் கேட்டு நிவர்த்தி செய்து கொள்ளுங்கள்.

இந்த ஆய்வின் நோக்கம்:

பாலி சிஸ்டிக் ஒவேரியன் சிண்ட்ரோம் என்னும் நோயானது தற்போது பெரும்பான்மையான பெண்களிடையே குழந்தையின்மை, ஒழுங்கற்ற மாதவிடாய்க்கான காரணமாக உள்ளது. இது இன்சுலின் ஹார்மோன் நம் உடலில் செயல்பட இயலாத தன்மையை ஏற்படுத்தி அதன் மூலம் கருமுட்டை வெளிபடுதலை தடுப்பதுடன், பெண்கள் உடலில் ஆண் இனப்பெருக்க ஹார்மோன் ஆண்ட்ரோஜனை அதிகப்படுத்துகிறது.

டி கைரோ ஐயனோசிடால் என்னும் மருந்தானது இன்சுலின் செயல்பாட்டினை அதிகரிப்பதன் மூலம், மாதவிடாயினை சரிபடுத்தி கருமுட்டை உருவாக்கம், வெளியேற்றத்தினை அதிகரித்து, ஹார்மோன் அளவுகளை கட்டுபாட்டிற்குள் கொண்டுவருகிறது.

இந்த ஆய்வில் டி கைரோ ஐயனோசிடால் மருந்தினை மெட்பார்மின் என்னும் மற்றொரு மருந்துடன் ஒப்பீட்டு ஆய்வும் நடைபெறும். இந்த ஆய்விற்கு "இன்ஸ்டியூசனல் எத்திக்ஸ் கமிட்டி"யின் சம்மதம் பெற்றிருக்கிறோம்.

ஆய்வு வடிவமைப்பு

இந்த ஆய்வில் கலந்து கொள்பவர்கள் மூன்று குழுக்களாக (A,B,C) பிரிக்கப்பட்டுள்ளனர். குழு A யில் உள்ளவர்கள் தற்போது நடைமுறையில் உள்ள மருத்துக்களும் (மெட்பார்மின்) பெறுவார்கள். குழு B யில் உள்ளவர்கள் டி கைரோ ஐயனோசிடால் என்னும் மருந்தினையும், குழு C யில் உள்ளவர்கள் மெட்பார்மின் மற்றும் ஐயனோசிடால் மருந்துகளையும் பெறுவார்கள்.

ஆய்வு நடைமுறைகள்

இந்த ஆய்வில் பாலி சிஸ்டிக் ஒவேரியன் நோய் கொண்ட அதிக எடையுள்ள, ஒழுங்கற்ற மாதவிடாய் கொண்ட, ஆண்டரோஜன் சுரப்பு அதிகமாக உள்ள, ஆண் போன்ற முடி வளர்ச்சி கொண்ட பெண்களிடம், இரத்த சர்க்கரை, கொழுப்பு, FSH, LH மற்றும் இண்சுலின் அளவுகள் மற்றும் அல்ட்ரா சோனோகிராம் (வயிறு ஸ்கேன்) போன்ற சோதனைகள் நடத்தப்பட்டு அதன் முடிவுகள் அடிப்படையில் வீருப்பப்படுபவர்கள் மூன்று குழுக்களாக பிரிக்கப்பட்டு, 12 வாரங்களுக்கு மருந்துகள் அளிக்கப்பட்டு அதன் முடிவில் எடை, சர்க்கரை, கொழுப்பு, LH அளவு, மாதவிடாய் ஒழுங்கு ஆகியவை குறித்து ஆய்வுகள் நடத்தப்படும். மேலும் 4^{th}, 8^{th}, 12^{th}, 16^{th}, 20^{th}, வாரங்களிலும் ஆய்வு மருத்துவர் மூலம் உடல் பரிசோதனைகள் நடத்தப்படும். நீங்கள் 5முறை ஆய்விற்காக மருத்துவமனை வரவேண்டும். இரத்த மாதிரிகள் இந்த ஆய்விற்காக இருமுறை (ஒவ்வொரு முறையும் 8மிலி இரத்தம்) எடுக்கப்படும். இந்த இரத்த பரிசோதனைகள் தங்கள் உடல் பரிசோதனைக்கு மற்றும் இந்த மருந்தின் பாதுகாப்பு மற்றும் பயனை அறிந்து கொள்வதில் முக்கியமானதாகும்.

இது தவிர தாங்கள் ஏதேனும் வேண்டாத விளைவுகளை உணர்ந்தால் உடனே எங்களுக்கு தெரியபடுத்தவும், நீங்கள் மீதியுள்ள மருந்துக்களை எங்களிடம் கொடுத்து விட வேண்டும். இது எங்களுக்கு மருந்தின் விளைவுகளை அறிய உதவும்.

ஆய்வினால் உங்களுக்கு ஏற்படும் நன்மைகள்

ஐயனோசிடால் மருந்து அதிக எடையினை குறைக்கவும், சர்க்கரை, கொழுப்பு, LH மற்றும் இண்சுலின் அளவுகளை கட்டுக்குள் வைக்கவும், மாதவிடாயினை ஒழுங்குபடுத்தவும் உதவுகிறது.

APPENDIX - V

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.R.M.Rajeshware
1 Year Post Graduate in MD Pharmacology
Institute of Pharmacology
Madras Medical College
Chennai 600 003

Dear Dr.R.M.Rajeshware,

The Institutional Ethics Committee has considered your request and approved your study titled **"EFFECT OF D-CHIRO INOSITOL IN POLYCYSTIC OVARY SYNDROME – A RANDOMIZED, OPEN LABEL, COMPARATIVE STUDY" NO. 06072016.**

The following members of Ethics Committee were present in the meeting hold on **05.07.2016** conducted at Madras Medical College, Chennai 3

1.Prof. C. Rajendran, MD.	Chairperson
2.Prof. Isaac Christian Moses,MD.,Dean(FAC)MMC ,Ch-3	Deputy Chairperson
3.Prof. Sudha Seshayyan, MD., Vice Principal, MMC.Ch- 3.	Member Secretary
4.Prof. B.Vasanthi,MD.,Prof of Pharmacology, MMC,	Member
5.Prof. P.Raghumani.MS., Professor of Surgery, Inst. of surgery	Member
6.Prof. Md Ali, MD.,DM., Prof & HOD of MGE, MMC,Ch-3.	Member
7.Prof. Baby Vasumathi.,MD, Director. Inst. of O&G,	Member
8.Prof. K.Ramadevi.,MD, Director, Inst of Bio-Chemistry, MMC,	Member
9.Prof. R.Padmavathy,MD., Professor, Inst.of Pathology, MMC,Ch	Member
10.Prof.S.Tito, MD, Director, Inst.of Inter Med, Ch-3.	Member
11.Tmt.J.Rajalakshmi, Junior Administrative Officer,MMC,Ch	Layperson
12.Thiru.S.Govindasamy., B.A.B.L., High Court, Chennai-1	Lawyer
13.Tmt.ArnoldSaulina, MA., MSW.,	Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee